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EFFECTS OF G-INDUCED STRESS ON PULMONARY CIRCULATION

Division of Pulmonary Diseases
of Mount Sinai Medical Center
Miami Beach, Florida 33140

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NOTICES

This final report was submitted by the Division of Pulmonary Diseases of Mount Sinai Medical Center, Miami Beach, Florida 33140 under contract F41609-74-C-0011, job order 7930-03-44, with the USAF School of Aerospace Medicine, Aerospace Medical Division, AFSC, Brooks Air Force Base, Texas. Dr. Sidney D. Leverett, Jr. (SAM/VNB) was the Laboratory Project Scientist-in-Charge.

When U.S. Government drawings, specifications, or other data are used for any purpose other than a definitely related Government procurement operation, the Government thereby incurs no responsibility nor any obligation whatsoever; and the fact that the Government may have formulated, furnished, or in any way supplied the said drawings, specifications, or other data is not to be regarded by implication or otherwise, as in any manner licensing the holder or any other person or corporation, or conveying any rights or permission to manufacture, use, or sell any patented invention that may in any way be related thereto.

The animals involved in this study were procured, maintained, and used in accordance with the Animal Welfare Act of 1970 and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources - National Research Council.

Human subjects gave voluntary informed consent; and monitoring of their rights was reviewed by the Human Rights Committee of Mount Sinai Hospital according to the guidelines published by the Department of Health, Education, and Welfare.

This report has been reviewed by the Information Office (OI) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.

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These investigations were concerned with the evaluation of the pulmonary circulation under mild gravitational stresses, such as water immersion and passive tilt to the upright position. Both anesthetized animals and conscious humans were studied. We extended our previous observations (made under Air Force Contract F41609-71-R-0039) that the standard USAF anti-G suit might be more efficient if inflated from below upwards, rather than from the abdominal bladder. Profiles of pressure inflation of the standard suit, during this contract year, confirmed our hypothesis that abdominal bladder pressure was

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Abstract (cont'd)

higher than calf or leg pressure during the inflation period. A modified anti-G suit was designed with pressure switches that enabled sequential filling from below upward. This suit was tested under 90° of passive tilt, and a higher cardiac output was produced after inflation of this modified suit than with the standard USAF anti-G suit. Such a modification might improve G tolerance and be useful for therapy of hypotensive states where venous return is reduced. Utilizing the rebreathing technique previously developed for pulmonary circulatory parameters under AF Contract F41609-71-R-0039--for which we also wrote the computer analysis program in Fortran--we measured the effects on pulmonary circulatory parameters of water immersion to the neck (NI). We thus demonstrated that, in the seated subject, such NI caused a significant increase in pulmonary capillary blood flow and diffusing capacity which persisted throughout the 4-hr immersion period. The lack of change in pulmonary tissue volume suggested that the central vascular engorgement so induced is not accompanied by extravasation of fluid into the pulmonary interstitial space. Our study thus supports the concept that, in the seated subject, the renal or hormonal effects of NI are mediated by a redistribution of blood volume, with a resultant central hypervolemia. We developed a bronchofiberscopic technique for sampling lobar oxygen, carbon dioxide, and nitrogen--as well as a computer program for calculating instantaneous respiratory exchange ratio. This ratio was proportional to that for ventilation to perfusion; and studies in anesthetized dogs gave expected values with change in posture and occlusion of a lobar pulmonary artery. Finally, we measured, for the first time, the fractionation of pulmonary blood volume in the intact animal. Of total pulmonary blood volume, pulmonary arterial blood volume constituted 28%; capillary blood volume, 22%; and venous blood volume, 50%.

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PREFACE

We gratefully acknowledge: the unstinting and devoted assistance, meticulous attention to details, and suggestions of Mr. Richard Dougherty, Chief Research Technician; and the contributions of Mr. Neal Atkins, Systems Analyst, for the computer programs used in these studies.

EDITOR'S NOTE: For further information on related research, the reader is referred to SAM-TR-75-25: Detection and Prevention of G-induced Regional Atelectasis, Edema, and Hypoperfusion, Dec. 1975.

CONTENTS

Figures

Contents, cont'd. (III)

Figures and Tables

Figure No.

Table No.

Figures and Tables

Figure No.

Table No.

Contents, cont'd. (IV)

Tables

EFFECTS OF G-INDUCED STRESS ON PULMONARY CIRCULATION

I. OVERVIEW OF RESPECTIVE STUDIES (Sections II - V)

INTRODUCTION

An anti-G suit as a personnel support garment is a well-accepted means of increasing acceleration tolerance. The gravity tolerance provided by anti-G suits has been related to: (a) an increased peripheral arterial resistance associated with elevation of arterial blood pressure; (b) a shortening of the heart-to-head distance; and (c) an increased venous return to the heart, secondary to emptying of the capacitance vessels of the lower extremities (4). Studies from this laboratory indicate that the anti-G suit elevates pulmonary capillary blood flow ($\dot{Q}_C$) during +1 G_z stress (3). In normal subjects, pulmonary ($\dot{Q}_C$) and cardiac output are equivalent. In seated subjects, however, no change is apparent in cardiac output when the standard USAF anti-G suit is inflated (2). If G tolerance is improved by increased venous return, then any anti-G suit that would provide an increase in cardiac output might be more effective under high gravitational acceleration stresses.

RESPECTIVE STUDIES

Section II of this study concerns an anti-G suit which has been modified so that the separated bladders are filled sequentially from calf to thigh to abdomen. The hemodynamic effects of the modified anti-G suit on capillary blood flow in subjects, during the supine resting position and after a 90° head-up standing tilt, are compared to a standard USAF anti-G suit inflation during the same maneuver; and this new anti-G suit was associated with a significant increase of pulmonary $\dot{Q}_C$, 1.7 liters/min greater than pulmonary $\dot{Q}_C$ produced by inflation of the standard USAF anti-G suit. In addition, the modified anti-G suit may be a useful device for treatment of circulatory shock and postural hypotension when the venous return is decreased.

Section III deals with the effects on the pulmonary circulatory parameters of subjects seated and immersed in water up to their necks.

EDITOR'S NOTE: The principal abbreviations, acronyms, and symbols used throughout this report are listed and briefly defined on the concluding pages (pp. 67-68).

Illustrations and tables have been grouped at the close of each report section (II - V).

This model simulates weightlessness and is known to be associated with a four-fold increase of sodium excretion by the kidneys. The data demonstrated that such "seated neck immersion" causes a significant increase of pulmonary $\dot{Q}_C$ and of the ratio of diffusing capacity to alveolar volume which persisted throughout the 4-hr immersion period. The lack of change of pulmonary tissue volume suggested that central vascular engorgement induced by seated neck immersion is not accompanied by extravasation of fluid into the pulmonary interstitial space. This study lends further support to the concept that the hormonal effects of seated neck immersion on the kidney are mediated by redistribution of blood volume with resultant central hypervolemia (1). These factors must be considered if it is decided to increase G tolerance by immersing subjects in a water-filled environment. Furthermore, this method ("seated water immersion to the neck") may constitute an alternative investigative tool for assessing the effects of volume expansion on renal electrolytes, homeostasis, and renin-aldosterone responsiveness. Also listed is a Fortran program for data processing of the rebreathing technique.

In Section IV, a bronchofiberscopic technique for measurement of lobar gas exchange is described. A mass spectrometer--used to sample continuously the tracheal and lobar gas for oxygen, carbon dioxide, and nitrogen--was connected to Teflon tubing (180 cm long, 0.15 mm i.d.). This tubing was passed through the inner channel of the bronchofiberscope so that its tip lay just within the instrument at its distal end. Lobar respiratory gas exchange ratio is proportional to the ventilation to perfusion ratio. We confirmed previous observations that lobar gas exchange ratio is increased in the nondependent lungs in the decubitus position and when a lobar artery is obstructed. A computer program was written to calculate continuously the lobar gas exchange ratio, breath by breath, and to give an estimate of the scatter of measurement throughout a single breath.

In Section V, fractionation of volumes of the pulmonary circulation in intact anesthetized dogs was accomplished by utilizing: an ether pneumotachographic or plethysmographic method, for pulmonary arterial blood volume (V_{PA}); a rebreathing technique, for pulmonary capillary blood volume (V_C); double-indicator dilution technique, for total pulmonary blood volume (PBV); and subtracting the sum of arterial and capillary volumes from the total, for an estimate of venous blood volume (V_V). Of the total PBV, V_{PA} constituted 28%; V_C, 22%; and V_V, 50%. This technique might be useful in ascertaining the behavior of the pulmonary circulation during future studies in anesthetized animals under higher gravitation stresses.

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II. EFFECTS OF SEQUENTIAL ANTI-G SUIT INFLATION ON PULMONARY CAPILLARY BLOOD FLOW IN MAN

ABSTRACT

The hemodynamic effects of an anti-G suit, sequentially filled from below upward (M-aG), were compared to those of the standard USAF anti-G suit (S-aG) in 10 men supine and under +1 G_z stress produced by 90° head-up passive tilt. The S-aG was found to fill from the abdominal bladder downward. The heart rate and the pulmonary capillary blood flow ($\dot{Q}_c$), as estimated by a nitrous oxide plethysmographic method, were used as criteria of effectiveness. Heart rate did not vary between the suits during the supine and upright studies. With subjects in the supine position, the first M-aG inflation induced a significant increase of pulmonary $\dot{Q}_c$, 2.5 liters/min above that of the S-aG inflation. In subjects after 90° head-up tilt, the M-aG inflation was associated with a significant increase of $\dot{Q}_c$, 1.7 liter/min greater than that of the S-aG inflation--thus indicating that sequential filling of the anti-G suit from below upward may further increase the G-protection compared to the standard garment. In addition, the modified anti-G suit may be useful in treatment of circulatory shock and postural hypotension when the venous return is decreased.

INTRODUCTION

The anti-G suit is a well accepted means of increasing acceleration tolerance in personnel. As stated in report section I, the G tolerance provided by these suits has been related to: (a) an increased peripheral arterial resistance associated with elevation of the arterial blood pressure; (b) a shortening of the heart-to-head distance; and (c) an increased venous return to the heart, secondary to emptying of the capacitance vessels of the lower extremities (13). Exposure to high sustained G_z (HSG) has, however, been shown to induce heart pathology in experimental animals (1). Therefore, newer devices for increasing tolerance of HSG should be evaluated (2) initially under lower $+G_z$ stress conditions.

The practice, in documenting the efficacy of proposed methods of improving G-tolerance, has been to evaluate--at +1 G_z--one or more of the three physiologic changes listed in the preceding paragraph. Sieker et al. (13), investigating experimental anti-G suits, demonstrated that the patterns of induced changes of arterial blood pressure and heart-to-head distance at +1 G_z differed from those at +3 G_z and above. They observed similar patterns of antecubital venous pressure changes at +1 and +3 G_z, however, and implied that the cardiac output at +1 G_z would be a reasonable predictor of its changes at higher G_z.

Previous studies in our laboratory (9, 11) have shown that the pulmonary capillary blood flow ($\dot{Q}_c$) does not change after inflation of the standard anti-G suit with subjects in the seated or supine positions; and we have proposed that the suit might be more effective if inflated sequentially from below and upward (9). To test this hypothesis, we modified an anti-G suit so that the separated bladders were filled sequentially--from calf, to thigh, to abdomen. We not only evaluated the hemodynamic effects of the modified anti-G suit on the pulmonary $\dot{Q}_c$ of subjects during supine resting posture (0 G_z) and after a 90° head-up (standing) tilt (1 G_z), but also compared them to the effects of the standard USAF anti-G suit inflation during the same maneuvers.

MATERIALS AND METHODS

Anti-G Suits

The standard anti-G suit utilized in this study was a USAF CSU-12/P suit, previously described in a journal article (2). The suit's 5 bladders were interconnected; there was one inflation inlet located in the abdominal bladder (Fig. 1). Inflation to 150 mmHg was achieved by an automatic pressure-regulating anti-G valve (Alar Products Inc., Cleveland, Ohio). Inlet air to the anti-G valve was supplied from an air compressor at 150 psi. The total inflation time was 3 sec.

The modified anti-G suit (Fig. 1) was constructed by disconnecting the 5 bladders of a standard anti-G suit and sealing the connections with contact cement. Each bladder was equipped with its own inlet (3/8 in. Tygon tubing and Swagelock 3/8 in. connectors). The right calf, right thigh, and abdominal bladders were equipped with pressure switches (#D2H-A3, Barksdale, Los Angeles, Calif.). From a pressure reservoir, the inlet tubing branched into the calf, thigh, and abdominal bladders via automobile tire stems. The calf bladders inflated first. When 150 mmHg was achieved, this pressure--sensed by the pressure switch at the calf--closed the solenoid valve at the bladder in that location (2-way solenoid valve #0695-5, Automatic Switch Co., Florham Park, N.J.), and opened the solenoid valve at the thigh bladder until a similar pressure was reached. Similarly, the abdominal bladder filled last. The total inflation time of the modified anti-G suit was 3 sec.

To measure the inflation profiles of the bladders of the two suits, 13-gage needles were inserted inside each of the bladders and connected to 3 variable reluctance differential gages (DP-7 Validyne, Northridge, Calif.). The suits were donned by one of the participants of this study, and pressure profiles of the two suits were recorded on multiple occasions on a Polygraph recorder (Model 78B, Grass Instruments Co., Quincy, Mass.).

Subjects

Ten men, ranging between 20 and 46 years and having body surface area between 1.6 m^2 and 2.2 m^2, were voluntary participants in this investigation. All subjects gave informed consent (see "Notices" page at beginning of report) and received financial remuneration for their participation. Prior to the study, all subjects underwent a brief orientation concerning the two anti-G suits and the nitrous oxide (N_2O) plethysmographic method for determination of pulmonary $\dot{Q}_c$. On at least two occasions, they had trial runs.

Protocol

Each subject, 1 to 2 hr after a light meal, donned either the standard USAF anti-G suit or the modified anti-G suit and rested supine within the body plethysmograph for 30 min before the beginning of the study. The type of anti-G suit was selected in random order. During the 2-min inflation period for the anti-G suit, inflation measurements were made during the second minute. Anti-G suit inflation was released immediately after the measurement was obtained.

After the initial 30-min rest period, the following hemodynamic measurements were obtained from the anti-G-suited supine subjects, at 15-min intervals (Fig. 2): (a) suit inflated; (b) suit deflated; (c) suit inflated; (d) suit deflated; and (e) suit inflated.

At 60 min after the initial measurement, the body plethysmograph was tilted to 90° head-up vertical position for 90 sec; and serial measurements were continued with the anti-G-suited subjects standing, 15 min later: (f) suit deflated; (g) suit inflated; (h) suit deflated; (i) suit inflated; and (j) suit deflated.

After the 5 "standing measurements," the body plethysmograph was tilted back to the horizontal position for 90 sec. After 15 min, measurements on anti-G-suited supine subjects were continued: (k) suit deflated; and (l) suit inflated. The subject was taken out of the body plethysmograph 3 hr after the experiment began, and repeated the same protocol 48 hr later wearing the alternate anti-G suit.

Method

Measurements of the pulmonary $\dot{Q}_c$, stroke volume (SV), and peak systolic output (PO) are based upon the body plethysmographic method originally described by Lee and DuBois (7) and recently adapted to a tilt-table body plethysmograph, the design and operation of which has

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NOTE: The total body plethysmograph used in these experiments did not permit measuring the seated +1 G_z.

previously been reported from our laboratory (4, 10). Briefly, the subject is enclosed within the airtight tilt-table plethysmograph, inspires a single breath vital capacity of an 80% N_2O and 20% O_2 mixture, and expires at a monitored and voluntarily controlled flow rate of 2 - 4 liters/min for 12 - 15 sec. Because N_2O is highly soluble in the pulmonary capillary blood, it is taken up as a function of the pulmonary $\dot{Q}_C$; the intra-alveolar pressure decreases and is reflected by a pulsatile fall of the body plethysmographic pressure. After inspiration of air the oscillations in plethysmographic pressure, due to the pulsations of the heart and large vessels, occur within the thorax and must be subtracted from the N_2O oscillations to obtain the true rate of N_2O uptake. Pulmonary $\dot{Q}_C$ then equals the N_2O uptake divided by the product of alveolar N_2O fraction and the solubility coefficient of N_2O in blood. Data are processed (10) by a PDP-12 digital computer (Digital Equipment Co., Maynard, Mass.). Since (in normal subjects) pulmonary $\dot{Q}_C$ equals 98.8% of the cardiac output (8), $\dot{Q}_C$ is assumed to be equivalent to the cardiac output.

In the presentation of data, mean values are followed by the standard error of the mean (SE) as an index of dispersion. The data were evaluated statistically by a Student's t-test for paired and unpaired values or, where appropriate, by 2-factor analyses of variance for experiments having repeated measurements on the same subjects (14). Differences with $P < .05$ were considered statistically significant.

RESULTS

Inflation Profiles

Shown in Figure 2 are typical inflation profiles for the standard USAF anti-G suit (S-aG) and for the modified anti-G suit (M-aG). The total inflation time for both suits was approximately 3 sec. In the S-aG inflation profile (Fig. 2, upper panel), it appears that the S-aG abdominal bladder inflates first and that at any time during inflation the abdominal bladder pressure is higher than in the calf or thigh bladders. The sequential filling of the M-aG is also depicted (Fig. 2, lower panel). The calf and thigh bladders inflate prior to the abdominal bladder inflation. (Actually, the rise in the calf bladder pressure occurred slightly before that of the thigh and, at any given time during inflation, the calf bladder pressure was either the same or slightly higher than that in the thigh bladders. This finding could be explained by the initial displacement of blood from abdomen to calf at the start of inflation, resulting in an increased calf diameter causing a pressure rise in the calf bladder which already has a low volume. The inflation profile of the modified anti-G suit--shown in the lower panel of Fig. 2--clearly shows that, although the total suit inflation time is similar to the standard suit, there is no possibility for trapping of blood in the lower extremities. The small discontinuity at the beginning of the abdominal bladder inflation profile is due to the subject tensing his abdomen, and is not present on all tracings.)

Heart Rate

The effects of the S-aG and the M-aG inflation on heart rate (HR) are presented in Figure 3. During all supine S-aG and M-aG measurements the HR was constant ($P > .05$), between 60 and 70 beats/min, and did not differ significantly from the two initial control supine measurements (63.8 ± 0.2 beats/min). The 90° head-up tilt resulted in a significant increase of HR to 82.9 ± 1.0 beats/min ($P < .001$). Both S-aG and M-aG induced a significant reduction of HR to 67.5 ± 1.0 beats/min ($P < .001$). During the entire study (12 pairs of HR measurements), no significant HR difference occurred between the two suits.

Pulmonary $\dot{Q}_C$

The mean supine control pulmonary $\dot{Q}_C$ in the first 15 min was 6.74 ± 0.10 liters/min (range 6.53 to 6.95); no significant difference occurred between these controls when the different anti-G suits were worn (Figs. 3 and 4). With subjects in the supine position, inflation of S-aG did not change the pulmonary $\dot{Q}_C$. The first M-aG inflation resulted in a significant ($P < .01$) increase of pulmonary $\dot{Q}_C$ (+2.50 L/min) above control. This $\dot{Q}_C$, after M-aG inflation, was also higher than that after S-aG inflation ($P < .05$). During the second inflation of the anti-G suits, the pulmonary $\dot{Q}_C$ was not different from the control values.

The 90° head-up tilt induced a significant ($P < .001$) reduction of pulmonary $\dot{Q}_C$ to a mean 2.73 ± 0.14 L/min (41% of control), a value identical for both days that the two anti-G suits were employed. In this posture, S-aG inflation induced a mean increase of $\dot{Q}_C$ of 0.50 L/min (+18%, $P < .05$), while M-aG increased $\dot{Q}_C$ by 2.68 L/min (+98%, $P < .001$). In the two upright M-aG inflations, the pulmonary $\dot{Q}_C$ differed significantly ($P < .01$) from that in the S-aG inflation. As shown in Figure 4, the pulmonary $\dot{Q}_C$ difference between the two suits was caused largely by more augmentation of SV by M-aG. The changes of peak systolic flow (Fig. 4: lower panel) paralleled the SV variations at all times during the 2-day study.

DISCUSSION

Wood and Lambert (18) determined relaxed $+G_z$ (3) tolerance by using blackout threshold in the human centrifuge and found that, when the calf and thigh bladders alone were inflated, only 0.2 G protection occurred. When the abdominal bladder alone was inflated, 0.6 G protection was obtained. When both leg and abdomen bladders were inflated together, however, 1.2 G protection was achieved, suggesting synergism between the abdomen and leg bladders. Sieker et al. (13) studied two new types of anti-G suits, the full bladder suit and the full pressure suit, both of which applied greater and more even pressure to the lower half of the body than did standard G-4A suit in use at that time. Both of these

suits provided greater G protection than the standard suit. More recently, Burton and Krutz (3) studied a pneumatic lever (Capstan) suit and determined relaxed tolerance for both rapid and gradual onset of acceleration. They confirmed that inflation of the leg bladders alone gave a 0.2 G protection, while inflation of the abdominal bladder alone increased G-tolerance to 0.7 G. However, 0.3 G protection was due to simple donning of the anti-G garment; and therefore they believed that the total G-protection of 1.2 G was a simple summation.

From this information, the 0.2 G protection provided by inflation of the leg bladders would appear to be insignificant in terms of total G-tolerance. However, Burton and Krutz (3)--using heart rate criteria and G-tolerance as a function of time--showed that inflation of the abdominal bladder has less protective value than the uninflated 5-bladder suit (standard USAF anti-G suit), and that the decrease in heart rate (compared to the uninflated suit) at +6 G_z for 60 sec was proportional to the inflation pressure in the leg bladders.

In the present study, we have demonstrated that inflation of the standard USAF anti-G suit creates, at any time during inflation, a higher pressure in the abdominal bladder than in the thigh and calf bladders. This phenomenon could impede the venous return from the lower extremities. We modified the suit to achieve a sequential filling of the bladders from calf to abdomen, and compared the two suits under low gravitational stress. The sequential inflation, from calf to abdomen bladder, of the modified anti-G suit was far more effective than the standard USAF anti-G suit in counteracting the depression of the pulmonary $\dot{Q}_C$ imposed by +1 G_z stress as developed after 90° head-up passive tilt.

It has been well established that the cardiovascular response to head-up tilt in normal man includes an increased heart rate and a disproportionally reduced SV, resulting in a fall of the cardiac output (5, 6, 11, 12, 15, 16, 17). Segel et al. (11) observed that a 90° head-up passive tilt causes a 41% increase of the HR, a 71% decrease of the SV, and a 61% fall of the cardiac output. In the present study, 90° head-up passive tilt induced a 30% increase of the HR, a 65% decrease of the SV, and a 59% fall of the cardiac output. These data establish the reproducibility of the circulatory changes induced by 90° head-up passive tilting.

Previous studies of the effects of the standard USAF anti-G suit, utilizing head-up passive tilt, have shown significant increase of the cardiac output. Weissler et al. (17) reported a 20% increase of the cardiac output during standard anti-G suit inflation in normal subjects in the passively tilted 60° head-up position. Utilizing essentially the same instrumentation as the present study, Segel et al. (11) reported a 31% increase of pulmonary $\dot{Q}_C$ after S-aG inflation in the 90° head-up passive tilt position, and observed the persistence of this effect over 20 min of S-aG inflation. In the present investigation, inflation of

the S-aG produced a similar increase of the cardiac output. In sharp contrast to the effect of this anti-G suit, inflation of the anti-G suit which was filled from below upwards induced a 98% increase of the cardiac output compared to the passive tilted value ($P < .001$). While the cardiac output after inflation of the S-aG remained at 50% of the supine control, inflation of the sequentially filled M-aG raised the cardiac output to 75% of the supine control. These changes were quite repeatable. The marked increase of the cardiac output was achieved by an increase of the SV (Fig. 4).

We also found that the 30% increase of the supine cardiac output was induced by the first inflation of the M-aG, but not by inflation of the S-aG--this was achieved by a rise in SV from 110 ml to 134 ml. The increase was not as reproducible as that after inflation in the 90^{o} head-up tilt. After the second supine inflation of both suits, the cardiac output did not change, possibly because of a tighter fit of the suit after the first inflation. This tighter fit would so redistribute the blood volume that less pooling of the blood might occur in the capacitance vessels of the legs. Furthermore, in all our subjects in supine and 90^{o} head-up tilt positions, a significant relationship existed between the SV and the peak systolic flow; and, after anti-G suit inflation, the differences of peak systolic flow between the two suits were similar to those of the SV. This information lends further support to the concept that the SV is the major determinant of the pulmonary capillary pulsatility, and that the gravitational force governing the regional pulmonary blood flow has little or no effect on the pulsatility (11).

Thus, the present study provides additional evidence that the leg bladder inflation is a crucial element of the anti-G suit for G-protection, and suggests that the sequential filling of the bladders from calf to abdomen may further increase G-tolerance by increasing the venous return to the heart. In addition, we have observed an increase of the supine cardiac output induced by the sequential anti-G suit inflation, a concept that could be used advantageously in circulatory shock associated with a decreased venous return. Although other modified suits have been described (J. Mitchell--Personal communication), this suit may have advantages because of simple construction and reported increases of cardiac output and stroke volume. (We have no explanation for the contradictory results of leg bladder inflation on increased G tolerance between previous experiments [centrifuge] and our observations.) The upright studies indicate that the modified anti-G suit might be useful in treatment of postural hypotension.

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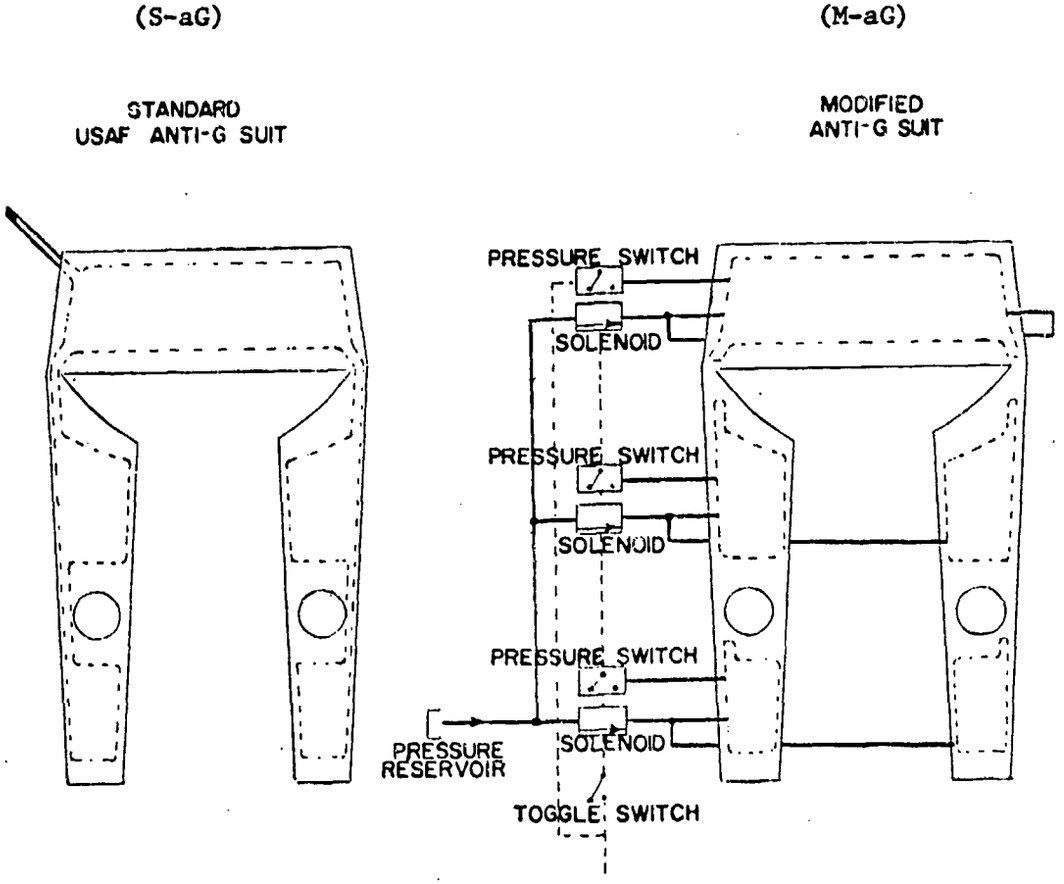

Figure 1. The S-aG suit CSU-12/P (left side) and the M-aG suit (right side) are compared in this study.

[The S-aG has only 1 pressure inlet, located in the abdominal bladder; the thigh and calf bladders are communicating with the abdominal bladder for inflation. In contrast, the M-aG has no communication between calf, thigh, and abdominal bladders. The 3 separate pressure inlets permit filling of the calf bladders first--and the thigh bladders, second; the abdominal bladder is inflated last.]

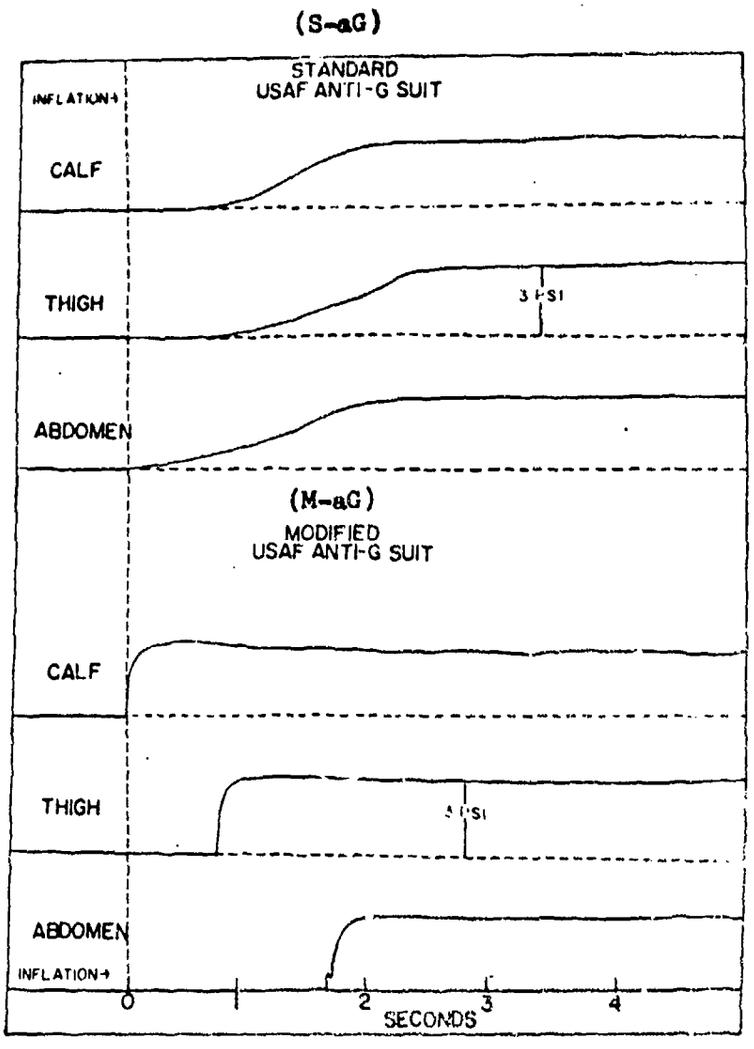

Figure 2. Inflation profiles of the S-aG (upper panel) and the M-aG (lower panel), obtained by monitoring pressure vs. time in the abdominal thigh, and calf bladders, respectively.

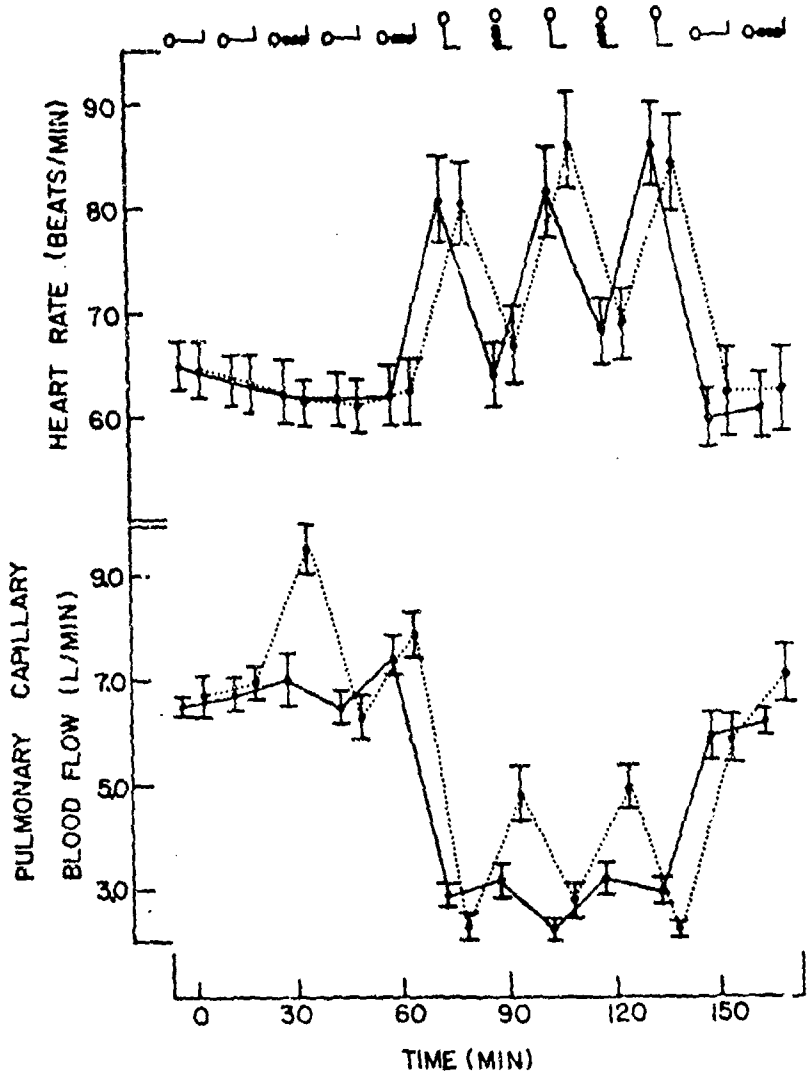

Figure 3. Mean values of heart rate and pulmonary $\dot{Q}_c$ in 10 normal subjects, at rest supine and 90° head-up vertical posture, before and during anti-G suit inflation ( ). [Vertical bars = SE; solid line = standard USAF anti-G suit; dotted line = modified anti-G suit; and L/min = liter(s) per min.]

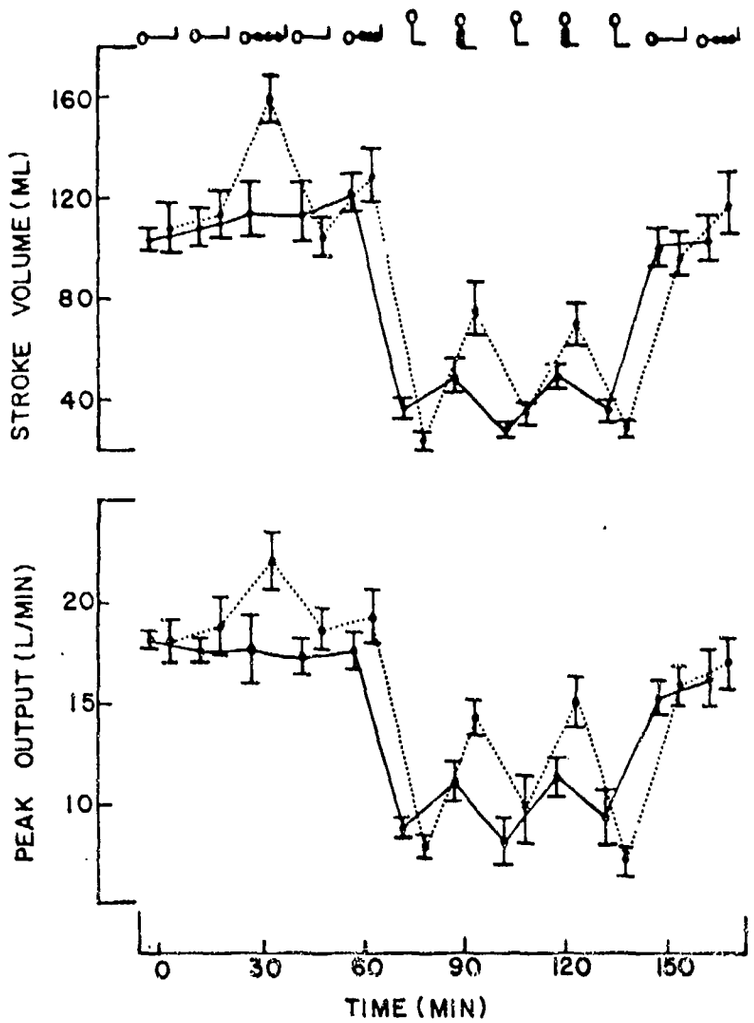

Figure 4. Mean values of stroke volume and peak systolic flow (peak output) in 10 normal subjects, at rest supine and 90° head-up vertical posture, before and during anti-G suit inflation (o—).

[Measurements were made during the second minute of a 2-min inflation period. Vertical bars = SE; solid lines = standard USAF anti-G suit; dotted line = modified anti-G suit; and L/min = liter(s) per min.]

III. EFFECTS OF WATER IMMERSION TO THE NECK (NI) ON PULMONARY CIRCULATION AND TISSUE VOLUME IN MAN

ABSTRACT

By utilizing the rebreathing of a gas mixture--containing C_2H_2, $C^{18}O$, He, O_2 and N_2--serial measurements of the pulmonary capillary blood flow ($\dot{Q}_c$), diffusing capacity per unit of alveolar volume (DL/VA), functional residual capacity (FRC), pulmonary tissue plus capillary blood volume (VTPC), and O_2 consumption ($\dot{V}O_2$) were obtained in 5 normal subjects under the following conditions: (a) 6 hr of sitting; (b) 4 hr of sitting while immersed in thermoneutral water to the neck; and (c) 4 hr of lying in thermoneutral water to the neck. "To-the-neck-immersion in water" (NI) of subjects was preceded and followed by 1-hr prestudy and 1-hr recovery. The measurements were made at 30-min intervals. Seated NI produced: a four-fold increase of sodium excretion ($U_{Na}V$); a 25% - 36% increase of $\dot{Q}_c$; a 45% - 59% increase of DL/VA; and a 30% - 36% decrease of FRC. These effects occurred as early as the first hour of NI, and persisted throughout the 4-hr study. Measurements of the $U_{Na}V$, $\dot{Q}_c$, and DL/VA during supine NI did not differ from those during seated NI. Throughout the seated, control, and NI periods, the $\dot{V}O_2$, heart rate, and VTPC remained constant. These data demonstrate that seated NI causes a significant increase of $\dot{Q}_c$ and DL/VA which persists throughout the immersion period. Furthermore, the lack of change of VTPC suggests that the central vascular engorgement induced by seated NI is not accompanied by extravasation of fluid into the pulmonary interstitial space. This study further supports the concept that the renal and hormonal effects of seated NI are mediated by a redistribution of blood volume with a resultant central hypervolemia. The use of seated NI may constitute an alternative investigative tool for assessing the effects of volume expansion on renal electrolytes, homeostasis, and renin-aldosterone responsiveness.

INTRODUCTION

Previous studies have demonstrated that, in subjects, NI results in a significant and reproducible natriuresis and diuresis, and a suppression of the renin-aldosterone system and ADH (11-15). Although the mechanisms involved have not been fully explained, evidence (2, 17)--based mostly on acute measurements--suggests that these effects are mediated in part by an immersion-induced redistribution of blood volume with a resultant central hypervolemia. Because of the invasive nature of methods previously utilized (2) and their possible influence on the factors measured (35), these alterations have not been assessed serially under steady-state condition over a prolonged period.

This serial assessment has been made possible by the recent development of a rapid, noninvasive, easily repeatable, and reproducible

method of measuring central hemodynamics (32). The current study was undertaken to characterize and define, under carefully controlled near-basal conditions, the effects of water immersion on: pulmonary capillary blood flow ($\dot{Q}_c$), diffusing capacity (DL), pulmonary tissue plus capiliary volume (VTPC), functional residual capacity (FRC), oxygen consumption ($\dot{V}O_2$), and heart rate. Furthermore, since the redistribution of blood volume which accompanies the transition from the upright to the supine posture is comparable to the redistribution induced by seated immersion (15, 17), measurements were made also during an identical period of supine immersion. It was anticipated that the increase in central blood volume, induced by assumption of the supine position per se, would preclude any further increase in central blood volume by the superimposition of water immersion. An additional advantage of supine immersion over supine non-immersed posture was the neutralization of the gravitational forces acting on the abdominal content and the rib cage to influence the position of the diaphragm (21).

MATERIALS AND METHODS

Subjects

Five men between the ages of 23 and 31 years were studied. All had a negative history for cigarette smoking, hypertension, cardiovascular disease, respiratory disease, and diabetes. Significant renal disease was excluded by documentation of a normal urine sediment and creatinine clearance. The cardiovascular status was judged normal by physical examination and electrocardiogram; the respiratory system was considered normal by physical examination and lung volumes. Closing volume performed on 3 of the subjects was also normal.

Water Immersion

Immersion was accomplished in a tank described in detail previously (11). The procedure for supine immersion has likewise been reported (15). A constant water temperature of $34^{\circ} \pm 0.5^{\circ}$ C was maintained by two heat exchangers, with a combined output of 13,500 Btu/hr--controlled by an adjustable temperature, calibrated control meter--with input derived from two thermistors immersed at different water levels.

Procedure

Each subject underwent not only a control study in the seated position (control), and a study during seated NI (seated immersion), but also a study during NI in the supine posture (supine immersion). Each study was separated by a 3- to 4-day interval. The experimental protocols on the 3 study days were similar: the subjects were studied after 10 hr of overnight fluid restriction. At 0800 hr, after voiding and

emptying completely his bladder, the subject assumed either the seated position (control and seated immersion) or the supine position (supine immersion) for 6 hr. During the control study, the subject sat quietly inside the empty immersion tank for 4 hr (0900 - 1300 hr). During seated immersion, the subject sat in the study tank and was immersed in water to the level of the sternal notch for an identical period. Both control and seated immersion studies were preceded and followed by 1 hr of quiet sitting outside the tank: prestudy (0800 - 0900 hr), and recovery (1300 - 1400 hr). During the supine immersion study, the subject first assumed the seated position for 1 hr outside the tank (0800 - 0900 hr), and thereafter assumed the supine position on a cot placed in the immersion tank for the next 6 hr (0900 - 1500). The cot was above the water level during the first (0900 - 1000) and last (1400 - 1500) hours, prestudy and recovery hours, respectively. During the 4 hr of supine immersion (1000 - 1400), the water was maintained at the sternal notch level, with the subject's entire body under water except for the face.

Prior to the study, each subject had a brief orientation in the rebreathing method; and each participated in trial runs on at least 2 occasions. All the subjects had participated in previous immersion studies and were thoroughly familiar with the protocol. During the study periods, measurements of pulmonary hemodynamics by the rebreathing method were obtained at 30-min intervals, starting 30 min after a change of position or condition was made.

Each subject stood briefly to void spontaneously at hourly intervals during the study. To maintain adequate urine flow, 200 ml of water were administered orally every hour during the study. Sodium, potassium, and creatinine were measured in aliquots of the hourly urine collections. A specimen of venous blood was also drawn at the end of each study for determination of serum creatinine and electrolytes. The subjects were weighed before and after each study.

Methods

Pulmonary capillary blood flow ($\dot{Q}_c$), diffusing capacity per unit of alveolar volume (DL/VA), functional residual capacity (FRC), combined pulmonary tissue plus capillary blood volume (VTPC), and O_2 consumption ($\dot{V}O_2$) were obtained by a rebreathing method utilizing a test gas mixture containing 0.5% C_2H_2, 0.3% $C^{18}O$, 10% He, 21% O_2, and balance N_2 (32). The rebreathing apparatus consisted of a 6-liter rubber bag attached to a 3-way valve (Quality Control, Inc., Malden, Mass.) and to a mixing pump (W. E. Collins, Inc., Boston, Mass.). Between the rubber bag and the mixing pump, two small canisters (2.5 cm i.d. x 8 cm in length)--containing soda lime granules as CO_2 absorbers--were added to the system in order to prevent the rise of end-tidal P_{CO_2} above 40 mm Hg. The dead space of the apparatus was 500 ml. Before each measurement, the bag was filled with 2.5 liters of gas mixture and allowed to equilibrate with the dead space of the apparatus for 2 min. The mixing flow rate in the

system was 1 liter/sec. The gas mixture was sampled at the breathing valve by a mass spectrometer (MGA-1100, Perkin-Elmer, Pomona, Calif.), intermittently before the test and continuously during the rebreathing procedure. During the bag mixing period, the subject breathed room air through the mouthpiece mounted on 1 orifice of the 3-way valve. Then the subject breathed from the rebreathing system, starting at the end of a normal expiration. The rebreathing maneuver consisted of 6 voluntary 2.0 - 2.5 liter breaths for 15 sec. The subjects were instructed to exhale passively to end-expiratory level during the maneuver. The data processing was done by a LINC-8 computer (Digital Equipment Co., Maynard, Mass.) connected to the mass spectrometer via a matching amplifier system (UMA, Electronic for Medicine, White Plains, N.Y.). [See Appendix A, of Section III.] The computer sampled at a rate of 7 points/sec, each point being corrected for He dilution--by using the initial inspired He concentration at each point for each gas. The disappearances of $C^{18}O$ and of C_2H_2 were calculated and displayed according to the method of Cander and Forster (6). Alveolar carbon monoxide values were corrected for back pressure CO in blood by assuming that the buildup occurred as a linear function of the number of tests (32). After the data were collected, the first three breaths were discarded because of wide variations of gas concentrations due to mixing; and the data were then analyzed over the last three breaths, during which variations of He concentration were minimal. The program displayed the $C^{18}O$ and C_2H_2 disappearance curves on the oscilloscope of the computer using a least squares fit. Correction was made for the start time to shift the C_2H_2 disappearance curve to display its intercept at time zero, a value which was a function of VTPC (6, 32). The heart rate was estimated by counting the radial pulse during the rebreathing procedure.

In the presentation of the data, mean values are followed by the standard error of the mean (SE) as an index of dispersion. The data were evaluated statistically by a Student's t-test for paired and unpaired values or, where appropriate, by two factor analyses of variance for experiments having repeated measurements on the same subject (34). If a significant effect was detected, a Newman-Keuls test was used to determine which treatment means were significantly different (34). Differences with $P < .05$ were considered significant.

After the procedure and the potential complications had been described in detail, permission for the study was obtained from each subject. The protocol was approved by the Human Experimentation Committees of the University of Miami School of Medicine and the Miami Veterans Administration Hospital.

RESULTS

Urinary Excretory Patterns

The effects of water immersion on sodium excretion and creatinine clearance are presented in Table 1 and Figure 1. During quiet sitting

(control), the subject's rate of sodium excretion ($U_{Na}V$) was constant, ranging from 64 to 81 meq/min. Seated immersion resulted in a progressive increase in $U_{Na}V$. During the last 3 hr of immersion, $U_{Na}V$ was three- to four-fold greater than during control. Recovery was associated with a decrease in $U_{Na}V$ compared to the final hour of seated immersion ($P < .05$). Supine immersion also resulted in a significant increase of $U_{Na}V$ that persisted during supine recovery. Creatinine clearance (C_{cr}) during control study was not significantly different from that in seated or supine immersion studies, ranging from 92 to 124 ml/min.

Metabolic Function

The results of oxygen consumption ($\dot{V}O_2$), used as an index of global metabolic function, are presented in Figure 2 and Tables 2-4. During the quiet sitting (control study) $\dot{V}O_2$ was nearly constant, ranging from 223 to 242 ml/min. During seated immersion and supine immersion, the $\dot{V}O_2$ did not differ from each other nor from the control study ($P > .05$).

Pulmonary Capillary Blood Flow ($\dot{Q}_c$)

Since in normal subjects $\dot{Q}_c$ equals 98.8% of the cardiac output (29), $\dot{Q}_c$ can be assumed to be approximately equivalent to the cardiac output. The results of $\dot{Q}_c$, cardiac index ($\dot{Q}_c/M^2BSA$), and heart rate (HR) are listed in Tables 2-4. Cardiac index (CI) is also plotted in Figure 3 for control and seated immersion. During the control study, $\dot{Q}_c$ ranged from 5.11 to 5.63 liters/min, CI from 2.72-3.01 liters/min/M^2, and HR from 61.2 to 64.0 beats/min. There was no significant change of $\dot{Q}_c$, nor HR, at any time during the 6 hr of quiet sitting (control study). Further, the prestudy of seated immersion and the prestudy of supine immersion did not differ from the control study. Seated immersion resulted in a significant increase of $\dot{Q}_c$ which persisted during the entire immersion period. The HR did not change during the entire study. For supine immersion, $\dot{Q}_c$ did not differ from seated immersion values, except during the recovery hour where $\dot{Q}_c$ was significantly higher than values during seated unimmersed period. However, in comparison to supine unimmersed period (prestudy), supine immersion induced a significant 12% increase of $\dot{Q}_c$ ($P < .05$).

Functional Residual Capacity

During the control study, FRC ranged between 2.71 and 2.97 liters BTPS (Tables 2 - 4). There was no significant difference among the mean values. In the prestudy and recovery studies of seated immersion, FRC was comparable to control ($P > .05$). However, seated immersion caused a significant decrease of FRC to 1.80 - 1.90 liters throughout the 4-hr period. Supine prestudy, immersion, and recovery also induced a decrease of FRC by an average of 0.40 liter without significant difference among these measurements.

Diffusing Capacity Per Unit of Alveolar Volume

Because of the variations of FRC (noted in preceding paragraph) and the constant volume of the rebreathing bag, the diffusing capacity of the lung (DL) was expressed per unit of alveolar lung volume (VA). The VA during the rebreathing procedure was taken as FRC plus one-half the tidal volume (28). Averaged, VA was: 4.0 liters STPD during control, prestudy, and recovery of seated immersion; 3.0 liters during seated immersion, and 3.5 liters during supine immersion (Tables 2-4; Fig. 3). During quiet sitting (control study), DL/VA ranged from 5.75 to 6.48 ml/min x mm Hg/liters ($P > .05$). Prestudy and recovery values of seated immersion were comparable to the control values ($P > .05$). Seated immersion induced a significant increase of DL/VA to a peak of 9.85 (58% above control) at hour 1 of immersion, with a mean sustained increment to 9.10 (46% above control) thereafter ($P < .05$). During supine prestudy, immersion, and recovery, DL/VA was significantly higher than during seated control ($P < .05$) but in the same range as the DL/VA of seated immersion ($P > .05$).

Pulmonary Tissue Plus Capillary Volume

No significant change of VTPC occurred during control and seated immersion (Tables 2 and 3; Fig. 2). During supine immersion, technical difficulties precluded measurements of VTPC in two of the subjects; and, consequently, VTPC is not reported in Table 4.

DISCUSSION

Previous studies of central hemodynamic events during water immersion in man have yielded conflicting results. Utilizing the acetylene rebreathing method, Kroetz and Wachter (26) demonstrated a 22% increase of $\dot{Q}_C$ during the initial hour of seated immersion in 3 subjects. Rennie et al. (30) demonstrated a 20% - 25% decrease in $\dot{Q}_C$ in man, with a concomitant 15% - 20% decrease in HR after 1 hr of seated immersion; but the water temperature in this study varied from 22° to 39° C. Hood et al. (22) assessed central hemodynamics in 5 subjects during an 8-hr immersion study in the semi-supine position, 30 cm below the water surface. These workers noted a decrease in HR without concomitant alterations in cardiac output, as assessed by the dye-dilution method. More recently, Arborelius et al. (2) demonstrated, by the dye-dilution technique, a 32% increase of cardiac output measured within 1 hr of seated immersion in 10 subjects. Our present studies extend the preceding reports; the effect of seated immersion on $\dot{Q}_C$ was observed repeatedly throughout the entire 4-hr immersion, with the subjects in a near basal and constant metabolic state. Seated immersion was associated with a significant 20% to 40% increase of $\dot{Q}_C$ in subjects as early as 30 min after initiation of immersion, with a persistence of the increase throughout the 4-hr immersion. Because the heart rate did not change, the effect was therefore entirely related to an increase of stroke volume.

The 35% - 60% increase of DL/VA observed in subjects during seated immersion is slightly larger than the results of Guyatt et al. (20), who reported a 22% mean increase of DL/VA during seated immersion. These authors used the single breath technique for obtaining the diffusing capacity. In the present study, VA during seated immersion was 0.9 liter smaller than quiet sitting. In other studies performed in our laboratory, such a variation of VA was found to increase the DL/VA from 6.45 (± 0.16) to 7.45 (± 0.12) ml/min x mm Hg/liters (+16%), without significant change of $\dot{Q}_c$, HR, and $\dot{V}O_2$. If this influence of lung volume on diffusing capacity is taken into account, DL/VA during seated immersion still remains 25% above control at a given VA.

Guyatt et al. (20) documented a 47% increase of the pulmonary capillary blood volume and suggested that the rise of DL/VA of immersion was caused by pulmonary vascular engorgement. The persistent increase of DL/VA throughout the 4-hr seated immersion (in the present study) is also consistent with a sustained engorgement of the pulmonary capillaries.

The 33% - 40% (1.0 liter) decrease of FRC during seated NI is slightly larger than the 13% (0.55 liter) decrease noted by Greene et al. (19) during seated water immersion to the xiphoid, and slightly less than the 46% (1.6 liter) observed by Agostini et al. (1) under experimental conditions similar to ours. Most of this decrease is due to a reduction of the expiratory reserve volume (1, 3). The present study demonstrates that these alterations persist throughout the 4-hr seated immersion.

In the present investigation, VTPC did not change with the different maneuvers; the values obtained were similar to those previously reported by Cander and Forster (6) and slightly higher than those observed earlier in this laboratory (32). A possible explanation for the latter difference could be the younger age of the subjects in the present study. Since VTPC has been described as a sensitive indicator of mild-to-moderate increase of lung water (18), the present findings indicate that the central vascular engorgement induced by water immersion is not accompanied by significant extravasation of fluid into the pulmonary interstitial space.

Gauer (16, 17) was the first to postulate that the redistribution of blood volume with a relative increase in central blood volume during water immersion may be mediated by an immersion-induced hydrostatic pressure gradient acting on the vascular column of the body. Subsequently, the roentgenkymographic works of Echt et al. (10) and Lange et al. (27), and the hemodynamic study of Arborelius et al. (2) have confirmed Gauer's hypothesis. During water immersion, a hydrostatic pressure gradient of 1 cm H_2O per centimeter of water depth is exerted on the body and displaces blood from the capacitance vessels of the lower extremities to the intrathoracic vascular bed. The additional volume of blood of the thorax is approximately 700 ml, 25% of which is located in the cardiac chambers. Concomitantly, the transmural central

venous pressure and the mean pulmonary artery pressure are increased by 15 mm Hg. These alterations of volume and pressure of the central circulation (particularly the cardiac chambers) are probably responsible for mediating the observed changes of cardiac output and stroke volume. The rise in DL/VA is due to an increase in pulmonary artery pressure observed during seated immersion (2), since DL/VA--and, specifically, the pulmonary capillary blood volume--are affected by pulmonary intravascular pressure changes (5, 9, 24, 31). The absence of significant increase of pulmonary interstitial fluid is not unexpected, since the pressure of seated immersion is only 6 mm Hg higher than those observed in the supine position.

During seated immersion of man, the mean hydrostatic pressure exerted on the thorax has been estimated to be near 20 cm H_2O (1, 8, 23). This increased pressure around the chest decreases the end-expiratory lung volume. Agostoni (1) considered this phenomenon as the main determinant of the decreased FRC in addition to the shift of blood in the thorax. The positive pressure applied to the chest wall during water immersion, and the atmospheric pressure of the airway, create a situation that is quite similar to negative pressure breathing. Agostoni and his coworkers (1) were able to reproduce the changes of lung volumes observed during seated immersion by breathing against a negative pressure of 20 cm H_2O; and Craig and Dvorak (8) were able to reverse completely the changes of lung volumes induced by seated water immersion, using positive pressure breathing. Furthermore, negative pressure breathing has been shown to increase the cardiac output (25), the diffusing capacity of the lung, and the pulmonary capillary blood volume (36). At a negative airway pressure of 20 cm H_2O, the changes of lung volume are similar to those in seated immersion. Furthermore, negative pressure breathing induces a natriuresis similar to that of water immersion (33). The noticeable differences between the two conditions are: the higher airway resistance observed during negative pressure breathing, a difference caused by the reduction of the extrathoracic tracheal lumen (1); and the support of the weight of the arms and shoulder girdle by the thorax during negative pressure breathing instead of by the water during seated immersion (8).

The transition from the upright to the supine posture is associated with a redistribution of blood volume, with an increase in central blood volume of approximately 400 ml (4). Thus, one would anticipate that the increase in central blood volume induced by assumption of the supine position per se may preclude any further increase in central blood volume by the superimposition of water immersion. The current demonstration that the transition from supine prestudy to supine immersion did not induce alterations in DL/VA is consistent with this interpretation. Supine posture, under steady-state conditions, does not cause significant change of $\dot{Q}_C$ (22). Accordingly, the small increased $\dot{Q}_C$ observed during supine immersion appears to have been induced by that type of immersion. Supine immersion to the sternal notch creates a mean

hydrostatic pressure of 7 cm H_2O on the thorax; this situation is analogous to a negative 7 cm H_2O pressure breathing (21), and could induce such a rise of $\dot{Q}_c$.

In conclusion, the present study demonstrates that, in subjects, NI in the seated posture results in significant increases in cardiac output and DL/VA which are sustained throughout the 4-hr immersion. The pulmonary tissue volume did not change, thus demonstrating that the central vascular engorgement induced by water immersion is not accompanied by extravasation of fluid into the pulmonary interstitial space. These observations further support the concept that the renal and hormonal effects of water immersion are mediated by a redistribution of blood volume with a resultant preferential central hypervolemia. The present demonstration that the central hypervolemia occurs without a concomitant increase in lung interstitial fluid volume suggests that, in contrast to saline infusion, immersion may constitute a safer alternative investigative tool for assessing the effects of volume expansion on renal electrolytes, volume homeostasis, and renin-aldosterone responsiveness.

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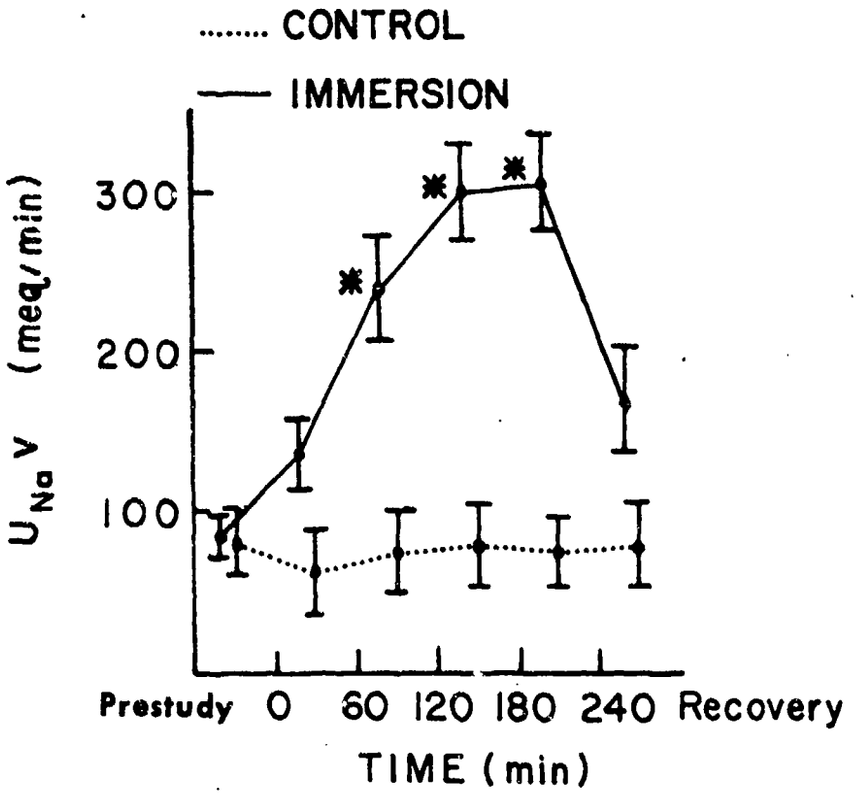

Figure 1. Effects on the $U_{Na}V$ of seated subjects undergoing water immersion to the neck (NI).
[Unimmersed = hatched line; immersion = solid line; bars = SE; and asterisks = statistically significant differences.]

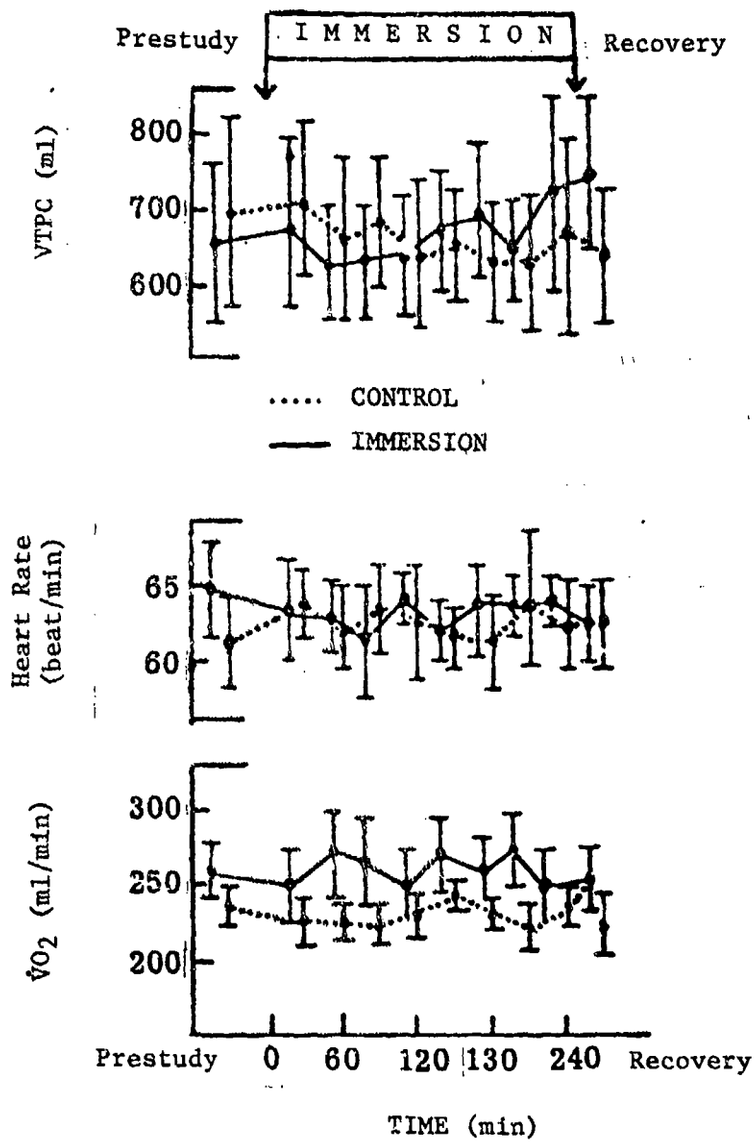

Figure 2. Effects on the VTPC, heart rate, and $\dot{V}O_2$, of seated subjects undergoing water immersion to the neck.
[Unimmersed = hatched lines; immersion = solid lines; and bars = SE. No statistically significant differences are present.]

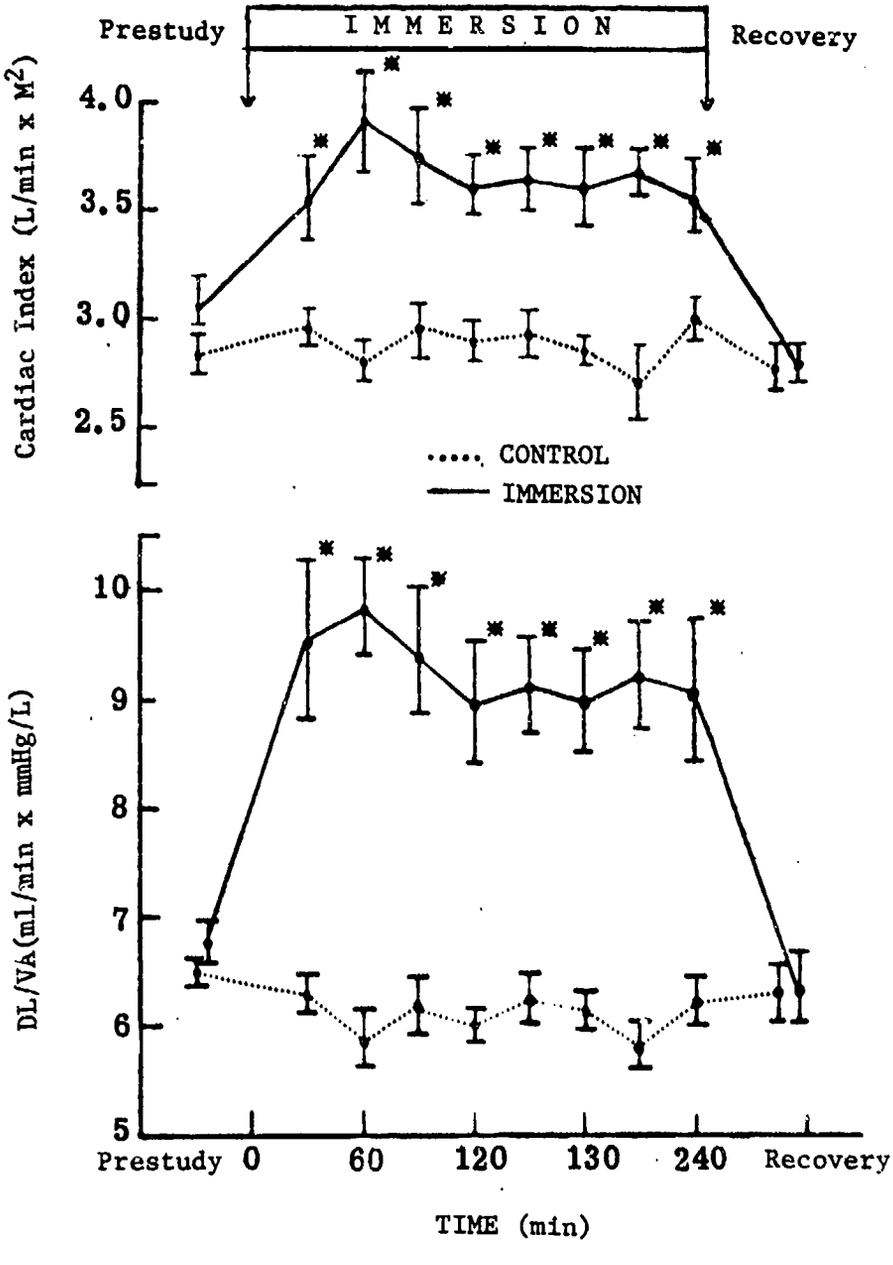

Figure 3. Effects on the cardiac index, and the diffusing capacity per unit of alveolar volume, of seated subjects undergoing water immersion to the neck.

[Control, prestudy, and recovery were also with the subjects in the seated position, but unimmersed. Unimmersed = hatched lines; immersion = solid lines; bars = SE; L = liter(s); and DL/VA = diffusing capacity per unit of alveolar volume.]

TABLE 1. EFFECTS OF IMMERSION ON SODIUM EXCRETION AND CREATININE CLEARANCE OF SUBJECTS

(Results are mean ±SE of 5 subjects)

		Prestudy	Time (hr) 1	2	3	4	Recovery
$U_{Na}V$ (meq/min)	Control	81.2 ±26.0	64.5 ±19.9	73.9 ±25.0	80.4 ±25.7	76.3 ±22.0	79.4 ±24.4
	Seated immersion	86.6 ±12.0	137.0 ±22.2	240.6 ±28.9	299.6 ±31.1	306.7* ±30.2	169.6 ±32.4
	Supine immersion	98.6 ±28.4	152.1 ±39.7	229.7* ±50.6	262.7* ±46.5	285.3* ±31.0	273.4*+ ±30.6
C_{cr} (ml/min)	Control	123 ±11	117 ±11	107 ±10	110 ±10	105 ±13	116 ±12
	Seated immersion	116 ±10	122 ±13	125 ±14	121 ±12	119 ±11	92 ±5
	Supine immersion	124 ±8	122 ±14	119 ±9	110 ±14	109 ±13	121 ±9

* $P < .05$ compared to control.
*+$P < .05$ seated immersion compared to supine immersion.
Hours 1 to 4 are periods in the immersion tank.

TABLE 2. EFFECTS ON SUBJECTS IN CONTROL STUDY

(Results are mean ±SE of 5 subjects)

	Control prestudy	Time (min) 30	60	90	120	150	180	210	240	Control recovery
O_2 consumption (ml/min)	237 ±11	227 ±16	224 ± 9	223 ±14	231 ±14	242 ±10	231 ± 9	223 ±15	236 ±11	224 ±20
Heart rate (beats/min)	61.2 ±3.1	63.6 ±2.2	62.0 ±2.6	63.2 ±2.9	62.4 ±3.7	61.4 ±1.9	61.2 ±3.1	64.0 ±4.4	62.4 ±3.1	62.4 ±3.1
Cardiac output ($\dot{Q}_c$) (liters/min)	5.30 ±0.31	5.52 ±0.24	5.29 ±0.32	5.52 ±0.37	5.55 ±0.26	5.44 ±0.22	5.35 ±0.31	5.11 ±0.46	5.63 ±0.37	5.11 ±0.29
Cardiac index (liters/min/M^2)	2.84 ±0.08	2.96 ±0.08	2.82 ±0.0[illegible]	2.95 ±0.12	2.90 ±0.09	2.93 ±0.10	2.86 ±0.06	2.72 ±0.17	3.01 ±0.09	2.78 ±0.10
DL/VA (ml/min x mmHg/liter) (STPD)	6.48 ±0.11	6.30 ±0.16	5.93 ±0.35	6.20 ±0.26	6.04 ±0.10	6.26 ±0.18	6.15 ±0.14	5.85 ±0.19	6.26 ±0.21	6.34 ±0.26
FRC (liters BTPS)	2.79 ±0.27	2.97 ±0.18	2.87 ±0.18	2.77 ±0.24	2.79 ±0.24	2.82 ±0.18	2.71 ±0.18	2.84 ±0.13	2.84 ±0.23	2.82 ±0.10
Pulmonary tissue + capillary vol (ml)	692 ±119	717 ±105	662 ±107	682 ± 84	639 ±102	657 ± 78	631 ± 83	631 ± 91	675 ±112	642 ± 93

TABLE 3. EFFECTS ON SUBJECTS IN SEATED IMMERSION STUDY

(Results are mean ±SE of 5 subjects)

	Seated prestudy	Time (min) 30	60	90	120	150	180	210	240	Seated recovery
O_2 consumption (ml/min)	260 ±17	251 ±23	276 ±32	267 ±28	251 ±25	271 ±25	261 ±20	274 ±25	249 ±24	255 ±19
Heart rate (beats/min)	64.4 ±2.9	63.2 ±3.3	62.8 ±2.2	61.2 ±3.5	64.0 ±1.7	62.0 ±1.8	63.2 ±2.8	63.6 ±1.8	64.0 ±1.7	62.4 ±2.4
Cardiac output ($\dot{Q}_c$) (liters/min)	5.77 ±0.35	6.70 ±0.56	7.39 ±0.70	7.05 ±0.66	6.80 ±0.51	6.85 ±0.54	6.80 ±0.54	6.88 ±0.44	6.74 ±0.55	5.22 ±0.31
Cardiac index (liters/min/M^2)	3.08 ±0.09	3.56 ±0.19	3.92 ±0.24	3.74 ±0.23	3.61 ±0.13	3.64 ±0.14	3.61 ±0.17	3.67 ±0.10	3.57 ±0.16	2.79 ±0.08
DL/VA (ml/min x mmHg/liter) (STPD)	6.77 ±0.18	9.57 ±0.71	9.85 ±0.44	9.45 ±0.56	8.99 ±0.54	9.13 ±0.42	9.01 ±0.46	9.22 ±0.45	9.10 ±0.63	6.37 ±0.31
FRC (liters BTPS)	2.85 ±0.22	1.81 ±0.19	1.90 ±0.17	1.87 ±0.14	1.90 ±0.17	1.84 ±0.19	1.80 ±0.21	1.89 ±0.14	1.89 ±0.29	2.92 ±0.24
Pulmonary tissue + capillary vol (ml)	657 ±103	674 ±122	624 ±70	632 ±67	638 ±79	674 ±78	698 ±89	642 ±68	725 ±130	747 ±106

TABLE 4. EFFECTS ON SUBJECTS IN SUPINE IMMERSION STUDY

(Results are mean ±SE of 5 subjects)

	Supine prestudy	Time (min) 30	60	90	120	150	180	210	240	Supine recovery
O_2 consumption (ml/min)	235 ±23	236 ±13	226 ±19	255 ±15	251 ±14	235 ±11	261 ±18	248 ±16	256 ±18	246 ±13
Heart rate (beats/min)	61.6 ±4.6	59.6 ±2.9	58.8 ±3.4	60.0 ±2.2	60.2 ±2.6	58.6 ±2.9	60.4 ±3.8	59.0 ±3.0	62.2 ±2.5	61.0 ±3.0
Cardiac output ($\dot{Q}_C$) (liters/min)	5.90 ±0.51	6.15 ±0.30	6.22 ±0.52	6.78 ±0.40	6.54 ±0.33	6.48 ±0.17	6.71 ±0.24	6.53 ±0.17	6.48 ±0.36	6.11 ±0.24
Cardiac index (liters/min/M^2)	3.14 ±0.16	3.29 ±0.10	3.34 ±0.24	3.63 ±0.17	3.51 ±0.15	3.49 ±0.11	3.55 ±0.16	3.48 ±0.10	3.59 ±0.09	3.29 ±0.06
DL/VA (ml/min x mmHg/liter) (STPD)	8.52 ±0.62	8.82 ±0.54	8.76 ±0.36	9.11 ±0.45	8.91 ±0.44	8.65 ±0.28	9.01 ±0.33	8.53 ±0.56	8.76 ±0.45	8.00 ±0.25
FRC (liters BTPS)	2.42 ±0.14	2.10 ±0.14	2.16 ±0.16	2.24 ±0.21	2.37 ±0.21	2.41 ±0.25	2.53 ±0.22	2.39 ±0.21	2.38 ±0.26	2.62 ±0.21

RE: SAM-TR-76-28
Appendix A (of Section III)

APPENDIX A: Fortran Program for Rebreathing Technique.

In order for comprehensive information on this research to be readily accessible, microfiche have been made of the above-mentioned material. The microfiche are available through:

The Aeromedical Library
Documentation Section
Brooks AFB, Texas 78235

IV. LOBAR MEASUREMENT OF RESPIRATORY QUOTIENT UTILIZING THE BRONCHOFIBERSCOPE

ABSTRACT

In this study concerning lobar measurement of respiratory quotient (R), a bronchofiberscope was used to permit placement of the sampling tip in lung segments and upper lobes. A Teflon catheter (0.15 mm i.d.), whose tip was placed just within the distal end of the inner channel of the bronchofiberscope, sampled lobar gas at 15 ml/min. A program written for a small digital computer analyzed the gases at 20 points/sec, computed R for each point, and then gave an average R and standard deviation for each breath. We performed experiments with this instrument in intact dogs (anesthetized with sodium pentobarbital), ventilated by phrenic nerve stimulation, preliminary to its contemplated use in humans. The variation among instantaneous R for each breath during tidal breathing was minimal and not statistically significant. With the test animals in the prone suspended position, R in the trachea and lobar bronchi ranged from 0.73 to 0.81 without systematic differences between upper and lower lobes. In the lateral decubitus position, lobar R was lower in the dependent than the nondependent lung. Obstruction of the left lower lobar pulmonary artery resulted in a significant increase of R in the left lower lobe, but not in other lobes. Obstruction of lobar bronchi by the bronchofiberscope or a balloon catheter, on the other hand, did not cause a decrease in regional R.

INTRODUCTION

In 1953, Martin et al. (1) showed that changes in oxygen and carbon dioxide concentrations within the lungs of conscious man could be detected by sampling the last third of an expiration with fine catheters inserted into the upper and lower bronchi. From multiple samples, they showed that the respiratory exchange ratio (R) was higher in the upper than the lower lung in man in the erect position; these differences were abolished by the supine position. Subsequently, Rahn et al. (2) demonstrated that any particular ventilation to perfusion ratio ($\dot{V}_A/\dot{Q}_c$) was associated with a unique respiratory gas exchange ratio. The higher the R, the greater the $\dot{V}_A/\dot{Q}_c$, and vice versa. They confirmed the positional alterations of R, in anesthetized dogs, as previously described by Martin et al. (1) in humans. West and Hugh-Jones (3) sampled lobar gas continuously in open-chest dogs by means of a rigid bronchoscope through which they connected a long sampling tube to a mass spectrometer. They found that occlusion of a bronchus produced a fall in respiratory gas exchange ratio, and obstruction of pulmonary artery produced a rise in R--changes that might be predicted from these physiologic stresses. Later, Hugh-Jones and associates (5, 6) measured lobar gas exchange by using this technique in humans, and described patterns of gas exchange similar to those observed in the animal experiment. They concluded that lobar gas sampling was useful in supplementing radiologic information in

the assessment of patients with bullae and emphysema, because it gave functional analysis of anatomic units. They further noted that, in such patients, radioactive Xenon scanning added little to the topographic information obtained by careful radiologic evaluation. In 1967, Hugh-Jones (6) theorized that the bronchoscopic technique had not found widespread utilization because endoscopy was usually done by surgeons, most of whom had little time to devote to respiratory physiology, and also because pulmonary physicians, who would be able to perform physiologic evaluations, had not yet learned the skill of bronchoscopy.

The recent widespread usage of the flexible bronchofiberscope by pulmonary physicians and the ability to sample gas readily from lobar bronchi in both upper and lower lobes has prompted us to reevaluate the determination of lobar gas exchange. The purpose of this study was to ascertain the feasibility of measuring lobar respiratory gas exchange ratios by a bronchofiberscopic technique in dogs--(a) in different postures and (b) after lobar pulmonary artery obstruction--preliminary to utilization of the method in humans.

METHODS AND MATERIALS

Thirteen mongrel dogs, weighing between 15 and 25 kg, were anesthetized initially with sodium pentobarbital, 15 - 25 mg/kg I.V. The dose was supplemented by 5- to 10-mg doses of this agent to maintain a light stage of anesthesia during the experimental period. The animals were intubated with an uncuffed oroendotracheal tube and placed in either the prone position, with the chest and abdomen suspended above the operating table, or in a lateral decubitus position. Respiration was assisted by means of transvenous PNS (7). The respiratory frequency and the tidal volume were adjusted by means of the stimulator, so that a Pa_{CO_2} between 35 and 40 mm Hg was maintained throughout the experiment. A catheter was placed into the right carotid artery for sampling arterial blood-gases. A triple lumen balloon catheter (U.S. Catheter and Instrument Corp., Billerica, Mass.) was placed into a left lower lobe pulmonary artery of 8 of the dogs.

Lobar Gas Sampling

A mass spectrometer (Perkin Elmer 1100 Medical Gas Analyzer, Pomona, Calif.) was used to sample continuously the tracheal and lobar gas for oxygen, carbon dioxide, and nitrogen. The instrument was connected to Teflon tubing, 180 cm long and 0.15 mm i.d. The instrument had a 90% response time of 69 msec. The transit time through the tubing was 127 msec at a sampling rate of 15 ml/min. The analog signals of the respiratory gases were inputted into an Oscilloscopic Recorder (DR-12, Electronics for Medicine, White Plains, N.Y.) and thence, via a matching amplifier (UMA, Electronics for Medicine), into a small digital computer (LINC 8, Digital Equipment Co., Maynard, Mass). For additional information on the Respiratory Exchange Ratio Program, consult Appendix A (of IV).

The gas fractions were digitalized by the computer at 20 points/sec. Generally, the computer was capable of storing data on 4 to 6 breaths during a given run. The R was computed at each point, as follows:

$$R = \frac{F_{ACO_2}}{F_{IO_2} \times \frac{F_{AN_2}}{F_{IN_2}} - F_{AO_2}}$$

The program gave the average R and SD for each breath. After typing the arteriovenous difference for O_2 across the lung into the computer, the ventilation perfusion ratio with its SD was calculated by the computer according to the equation:

$$\frac{\dot{V}_A}{\dot{Q}_c} = \frac{1.21 \times (C_{aO_2} - C_{\bar{v}O_2})}{F_{IO_2} \times \frac{F_{AN_2}}{F_{IN_2}} - F_{AO_2}}$$

Procedure

The Teflon sampling catheter was inserted through the inner channel of an Olympus BF-52 bronchofiberscope (Olympus Corp., New Hyde Park, N.Y.) so that its tip lay just within the bronchofiberscope at its distal end. The catheter had to be kept within the inner channel; for, according to preliminary experiments, as soon as the tip of the catheter contacted the bronchial mucosa, the sampling flow ceased due to secretions blocking the catheter.

Sampling of respiratory gases in the trachea and lobar bronchi was first conducted with the test animal in the prone suspended position. After this procedure was completed, the trachea and the left and right lower lobar bronchi were sampled, and the balloon catheter in the left lower lobar artery was inflated to occlude the blood supply while the measurements were repeated. Finally, the dog was placed in the left lateral decubitus position, and tracheal and lobar respiratory gas were sampled. Complete obstruction of a lobar bronchus was accomplished by inflation of a balloon at the distal end of the bronchofiberscope. Gas was sampled distal to the obstruction for determination of respiratory gas exchange.

The mechanical effects of partial airway obstruction were tested by measuring pressure distal to the bronchofiberscope by means of a catheter tip manometer (4F, Millar; Millar Instruments, Inc., Houston, Tex.) placed within the inner channel. Pressures were measured in a segmental bronchus, lobar bronchus, and trachea. The pressure in the trachea was also measured by the catheter tip manometer alone. The effects on tidal volume of both the catheter and the bronchofiberscope were measured by using a "T" adaptor (8) to record tidal volume by means of a spirometer.

RESULTS

Figure 1 depicts tracings from the oscilloscope of the digital computer for CO_2, O_2, and N_2 (per cent), as well as instantaneous R on a breath-by-breath basis. In any given breath, the variation of R during steady-state conditions was minimal. In 11 prone dogs, the means of the standard deviations of the mean among the trachea and lobar bronchi ranged from 0.01 to 0.03. For a given breath, the slope of R over time varied in a random fashion; both positive and negative slopes occurred in approximately equal frequency. For the 11 dogs, the mean slopes ranged from -0.010 to +0.003 R/sec in the trachea and lobar bronchi.

No difference existed in tracheal R when sampled by the catheter (1 mm o.d.) or after introduction of the bronchofiberscope (5.8 mm o.d.). Also, no significant differences in R were found among the trachea and lobar bronchi in 11 dogs in the prone position (Table 1). Ventilation to perfusion ratios were calculated in 4 of these animals (Table 2), and these ratios were even through the lung. R was significantly higher in the nondependent than the dependent lung when the dogs were placed in the lateral decubitus position ($P < .01$) (Table 3).

R was not altered by different placements of the bronchofiberscope within a particular lobar bronchus. Complete occlusion of a lobar bronchus by a balloon cuff effected no change in R measured distal to the obstruction. When the bronchofiberscope was wedged into a subsegmental bronchus, R dropped as much as 30%.

Within 10 to 15 min following obstruction of the left lower lobar artery by a cardiac balloon catheter, mean R in 7 dogs rose from 0.77 to 0.97 ($P < .001$) (Table 4); but no change of R occurred in the right lower lobe bronchus or trachea. After relief of the obstruction, the values of R returned toward baseline. The ventilation to perfusion ratio determined in 4 of the dogs rose from 0.56 to 1.46.

Partial occlusion of the airway by the bronchofiberscope produced a progressive increase in distal pressure during placements from the trachea to the segmental bronchus (Fig. 2). This increase occurred while PNS voltage and frequency were maintained constant. Tidal volume was the same before and after introduction of the bronchofiberscope into the trachea.

DISCUSSION

The present experiments indicate that the bronchofiberscope is an adequate instrument to direct a catheter for lobar gas sampling. Using the data of Rahn et al. (2), it can be calculated that the bronchofiberscope reduced the cross-sectional area of the bronchi by an average of 31%. Using their assumptions that alveolar pressures are not altered by the partial airway obstruction produced by the bronchofiberscope and that airflow is linear, the alteration in ventilation under these conditions can be calculated by application of Poiseuille's law. These calculations indicate that the bronchofiberscope should diminish lobar ventilation by 55%. Compared to the sampling catheter alone, however, the bronchofiberscope did not alter tracheal R, and values of R in the tracheal and lobar bronchi were similar. The explanation for the discrepancy between the experiment and calculated data lies in the false assumption that the alveolar pressure is not affected by the partial obstruction. Ventilation was assisted by PNS in the present studies. During increasing grades of obstruction induced by the placement of the bronchofiberscope into smaller airways, distal pressures rose in the airway occluded. Thus, although lobar ventilation was not directly measured, the finding of a localized increased alveolar pressure and lack of change in R would be consistent with preservation of ventilation due to interdependence (9). The latter phenomenon would also facilitate collateral ventilation into the obstructed lobe. Placing the bronchofiberscope in the trachea did not alter tracheal R or tidal volume. The reason for this finding may lie in previous observations that mild-to-moderate resistive loads to breathing in man cause a drop in frequency but a slight increase in tidal volume (9, 10). With diaphragmatic pacing in our animals, frequency is kept constant so that ventilation, and hence R, remain unchanged.

Our method of transvenous PNS via passage of the pacing catheter through the right internal jugular vein causes contraction of the right leaf of the diaphragm and, to a lesser extent, the left leaf (7). Daggett et al. (12) showed that right phrenic nerve pacing in dogs effected both an increase in ventilation and perfusion in the right lung--but that the $\dot{V}/\dot{Q}$ ratio, as determined by radioactive xenon scan, was the same in both lungs. Our data on lobar R and $\dot{V}_A/\dot{Q}$ confirm their findings and extend the even distribution of $\dot{V}_A/\dot{Q}$ to the lobes as well. Minh et al. (13) found large variations in regional transpulmonary pressure and thoracic configuration during pacing of the right phrenic nerve. They proposed that lobar interdependence might be a mechanism for maintaining stability in ventilation perfusion equality during unilateral electrophrenic respiration.

Our mean values for R in the prone position were similar to those of Rahn et al. (2) for R in the supine position. However, the latter reported a higher R in the upper than the lower lobes, a phenomenon which we did not observe. These authors used a continuous sampling

method and analyzed a single sample. As they pointed out, this contamination by inspiratory gas would tend to reduce the differences in R that exist between lobes. The explanation for the more even distribution of R in the present study might be in our method of assisting ventilation by phrenic nerve pacing, which has been shown to improve arterial oxygen tension and alveolar-arterial O_2 gradient as compared to spontaneous breathing (13). Finally, we measured R in the suspended prone position, whereas Rahn et al. (2) studied the dogs in the supine position. The latter position could have produced pulmonary distortion because of the weight of the mediastinum.

The respiratory exchange ratio was consistently higher in the nondependent than the dependent lobes in the lateral decubitus position. This finding confirms the more pronounced effects of gravity on blood flow than ventilation, as previously reported by others (1, 2).

Prolonged expiration is associated with a fall in R as a function of time (10). In humans, this change in slope between 750 ml and 1250 ml of alveolar gas is mainly due to changes of gas tensions due to gas exchange which takes place during expiration (11). No consistent pattern in the slope of lobar R over time was seen during tidal breathing in the dogs, probably because the short period of expiration masked such changes. Thus, we did not find it necessary to correct R for time of breathholding, as proposed by Meade et al. (15).

The increase of R in the lobe caused by temporary pulmonary arterial occlusion was predictable. The ventilation to perfusion ratio rose an average of 261%, thus confirming the observations made by West and Hugh-Jones (3) in an open-chest dog model. These studies indicate that measurement of lobar R might be useful in the diagnosis of pulmonary emboli.

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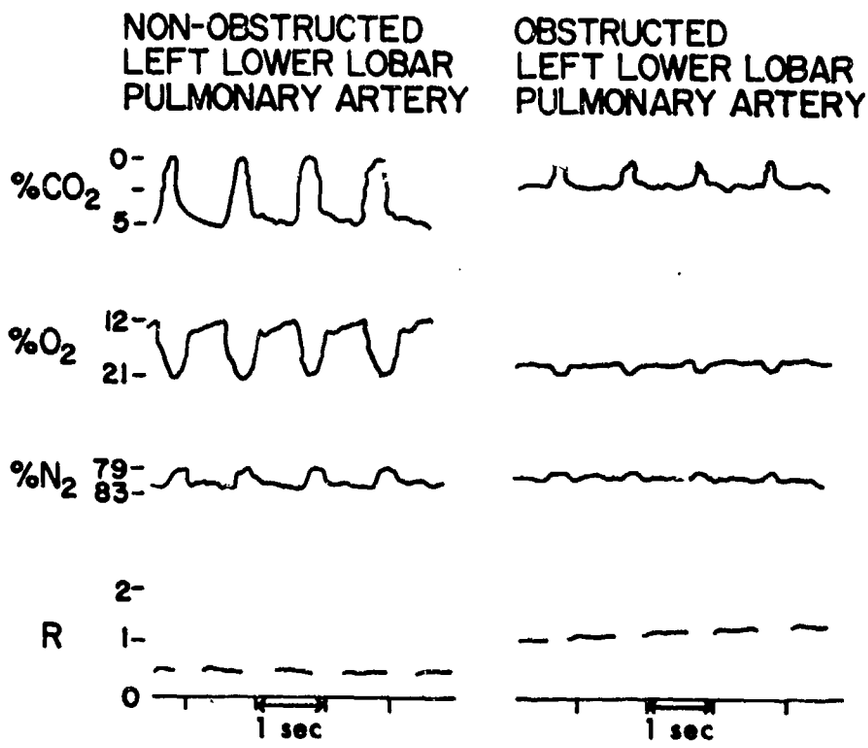

Figure 1. CO_2, O_2, N_2, and R from left lower lobe, as shown in tracings from the oscilloscope of the digital computer.
(The left panel shows gas concentrations and R in the left lower lobe. The right panel shows these parameters after obstruction of the left lobar artery by a balloon catheter.)

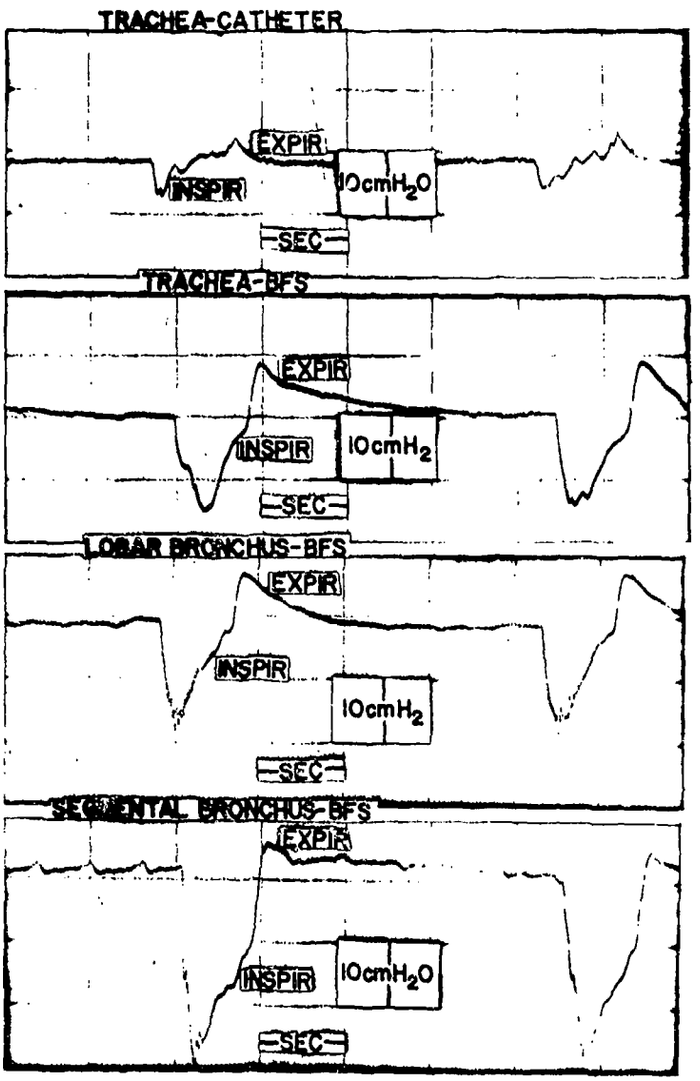

Figure 2. Effects upon airway pressures as result of obstruction by the catheter in the bronchofiberscope (BFS).
(With increasing degrees of obstruction to the airway produced by the BFS, distal pressure rises.)

TABLE 1. RESPIRATORY EXCHANGE RATIO IN SUSPENDED PRONE POSITION*

	Mean	(SD)
Trachea	0.79	(0.08)
Right upper lobe	0.81	(0.14)
Right middle lobe	0.78	(0.10)
Right lower lobe	0.81	(0.08)
Left upper lobe	0.80	(0.15)
Left middle lobe	0.73	(0.14)
Left lower lobe	0.76	(0.11)

*Mean of 11 dogs.

TABLE 2. VENTILATION TO PERFUSION RATIO IN SUSPENDED PRONE POSITION*

	Mean	(SD)
Trachea	0.74	(0.13)
Right upper lobe	0.70	(0.13)
Right middle lobe	0.53	(0.09)
Right lower lobe	0.74	(0.19)
Left upper lobe	0.73	(0.14)
Left middle lobe	0.73	(0.22)
Left lower lobe	0.83	(0.18)

*Mean of 4 dogs.

TABLE 3. RESPIRATORY EXCHANGE RATIO IN LATERAL DECUBITUS POSITION*

	Mean	(SD)
Nondependent lung		
Upper lobe	1.06	(0.14)
Middle lobe	0.94	(0.06)
Lower lobe	0.94	(0.16)
Dependent lung		
Upper lobe	0.86	(0.17)
Middle lobe	0.84	(0.11)
Lower lobe	0.87	(0.15)

*Mean of 4 dogs.

TABLE 4. EFFECTS OF LOBAR ARTERIAL OBSTRUCTION ON R AND $\dot{V}_A/\dot{Q}$

	Control		Obstruction		Recovery	
			R*			
Left lower lobe	0.77	(0.17)	0.97	(0.15)	0.77	(0.16)
Right lower lobe	0.82	(0.20)	0.73	(0.13)	0.74	(0.11)
Trachea	0.81	(0.15)	0.72	(0.12)	0.76	(0.12)
			$\dot{V}_A/\dot{Q}$+			
Left lower lobe	0.56	(0.12)	1.46	(0.32)	0.49	(0.25)
Right lower lobe	0.57	(0.15)	0.44	(0.14)	0.47	(0.21)
Trachea	0.55	(0.15)	0.42	(0.14)	0.45	(0.20)

*Mean (and SD) of 7 dogs.

+Mean (and SD) of 4 dogs.

RE: SAM-TR-76-28
Appendix A (of Section IV)

APPENDIX A: The Respiratory Exchange Ratio Program describes this program in detail, and includes flow charts.

In order for comprehensive information on this research to be readily accessible, microfiche have been made of the above-mentioned material. The microfiche are available through:

The Aeromedical Library
Documentation Section
Brooks AFB, Texas 78235

V. VOLUMES OF PULMONARY VASCULAR COMPARTMENTS IN INTACT DOGS

ABSTRACT

The functional volumes of the pulmonary vascular bed were measured in intact anesthetized (25 - 50 mg/kg sodium pentobarbital) dogs at functional residual capacity. Total pulmonary blood volume was determined by a double-indicator dilution technique. Pulmonary arterial blood volume was calculated as the product of pulmonary blood flow and mean pulmonary arterial transit time obtained from an ether injection method, and pulmonary capillary blood volume was measured by a rebreathing technique. Pulmonary venous volume was calculated by subtracting pulmonary arterial and capillary blood volumes from total pulmonary blood volume. In 10 dogs, mean (± SE) total pulmonary blood volume was 251 (± 26) ml (100%); mean pulmonary arterial blood volume, 71 (± 10) ml (28%); mean pulmonary capillary blood volume, 55 (± 7) ml (22%); and mean pulmonary venous blood volume, 125 (± 20) ml (50%). Preliminary experiments with continuous infusion of 5-hydroxy-tryptamine into the pulmonary artery at a rate of 10 μg/min/kg indicate that, in this dosage, this agent causes pulmonary arterial vasoconstriction with a decrease in pulmonary arterial blood volume, but no consistent changes in pulmonary capillary and venous blood volumes.

INTRODUCTION

The anatomic compartments of the pulmonary vascular bed are composed of the arterial, capillary, and venous segments. Ample information is available about blood flow through the pulmonary vessels, about pressure drop across the pulmonary circulation and, thus, about pulmonary vascular resistance in normal animals and humans. Similarly, the effects of pharmacologic agents, hypoxia, and acidosis on pressure-flow relationships have been well studied in the past. The introduction of the double-indicator dilution technique (1) has made it possible to reproducibly measure total pulmonary blood volume--which is the volume of blood contained in the pulmonary circulation between the pulmonic valve and left atrium. However, the differential volumes of the pulmonary vascular bed (namely, pulmonary arterial, capillary, and venous blood volumes) have thus far not been determined in intact animals or in humans. Previous studies on the volumes of the pulmonary vascular compartments have been restricted to physiologic measurements in excised lungs or lung lobes (2), or to post-mortem examinations (3). These measurements may not accurately reflect the functional vascular volumes present in vivo. Usage of the ether injection method for the determination of pulmonary arterial transit time together with the measurements of pulmonary blood flow allows the calculation of pulmonary arterial blood volume (4) which, in conjunction with the measurements of pulmonary capillary blood volume (8) and total pulmonary blood volume, makes it possible to calculate the functional volumes of the pulmonary vascular

bed. The present investigation was undertaken to determine, with these techniques, the compartmental volumes of the pulmonary circulation in intact anesthetized dogs, and possibly to change these volumes by infusion of 5-hydroxy-tryptamine. Only preliminary results will be reported, because the experiments were not complete at the time of this report.

METHODS

Mongrel dogs were anesthetized with 25 - 50 mg/kg sodium pentobarbital and intubated with a cuffed orotracheal tube. Catheters were placed: in the external jugular vein; in the superior vena cava; and in the pulmonary artery; as well as in the left atrium, by a retrograde approach from a femoral artery. A bipolar electrode was also placed in the superior vena cava for transvenous phrenic nerve stimulation (PNS) which was used for ventilatory support (5). The animal was then placed in a body plethysmograph (6) and the endotracheal tube was connected to a perforation in the door of the plethysmograph, provided with a three-way valve (which allowed the dog to breathe room air), to be connected to a 1000 cc giant syringe or to be occluded at the mouth. All catheters were led to the outside through perforations in the door. The connections were provided with three-way stopcocks so that the different catheters could be used: for pressure readings with strain gages at midchest level (Statham P 23); for withdrawal of blood through densitometers, using Harvard infusion pumps; or for rapid injection with an automatic injector (Cordis, type 97-E-7). An electrocardiogram was continuously recorded. Total pulmonary blood volume and pulmonary blood flow were determined by a double-indicator dilution technique (1). Indiocyanine (1 cc) was injected into the superior vena cava, and blood was withdrawn simultaneously from the pulmonary artery and left atrium through densitometers (Gilford, Model 103 TR), using identical flow rates and catheters of matching length and diameter. Pulmonary arterial transit time was determined by the ether injection technique which has been described previously in detail (7). Pulmonary capillary blood volume, pulmonary $\dot{Q}_c$, and alveolar volume were determined by the rebreathing method (8) already described in detail (in report section III). Rebreathing of the gas mixture was achieved by the use of the giant syringe with a tidal volume of 500 ml--between 250 ml below and 250 ml above functional residual capacity (FRC)--at a rate of 0.5 Hz. The run was terminated after 15 sec. The ether transit time was determined during apnea, whereas total pulmonary blood volume was measured both during apnea and during rebreathing. Pulmonary venous blood volume was calculated by subtracting the pulmonary arterial blood volume and pulmonary capillary blood volume from total pulmonary blood volume. Measurements were made in duplicate. All signals were recorded simultaneously on an Electronics for Medicine 12-channel recorder and on magnetic tape (Technical Measurement Corporation) for off-line computer analysis, or directly fed into a small digital computer (LINC 8, Digital Equipment Corp., Maynard, Mass.) via A/D converters for on-line computer analysis (indicator dilution, ether transit time, rebreathing technique).

In 10 dogs, measurements were made at FRC. In 7 other dogs, measurements were made before and during the infusion of 5-hydroxy-tryptamine into the external jugular vein at a rate of 10 μg/min/kg. In these animals, specific respiratory system conductance (using the alveolar volume obtained from the rebreathing technique for calculations) and static lung compliance were also measured before and during drug infusion by previously described methods (9).

RESULTS

Listed in Table 1 are the mean values (with 1 SE) in 10 dogs at FRC, for pulmonary blood flow ($\dot{Q}_p$), pulmonary capillary blood flow (Q_c), heart rate (HR), mean pulmonary arterial pressure ($\bar{P}_{PA}$), mean left atrial pressure ($\bar{P}_{LA}$), pulmonary vascular resistance (R_{PV}), total pulmonary blood volume (PBV), pulmonary arterial blood volume (V_{PA}), pulmonary capillary blood volume (V_C), and pulmonary venous blood volume (V_v). The relative distribution of compartmental blood volumes was 28% for V_{PA}, 22% for V_C, and 50% for V_v.

The effect of 5-hydroxy-tryptamine on central hemodynamics of 7 dogs is shown in Table 2. In addition to the parameters shown in Table 1, Table 2 contains mean values for specific respiratory system conductance (SG_{rs}) and static lung compliance (C_{st}). The values in parentheses represent 1 SD. The mean control values for the different parameters in this group were similar to those listed in Table 1 for the first 10 animals. During 5-hydroxy-tryptamine infusion, there was a marked increase in R_{PV} and $\bar{P}_{PA}$, with only a slight increase in $\dot{Q}_p$ and left atrial pressure. A decrease occurred: in mean PBV, 6%; in mean V_{PA}, 18%; and in mean V_v, 6%; but V_C increased 14%. Mean specific respiratory system conductance fell to 36% of control values, whereas static lung compliance was unchanged.

DISCUSSION

These are, to our knowledge, the first measurements of the functional volumes of the pulmonary vascular bed in intact animals. Sackner and DuBois (10) calculated from direct measurements of V_v and V_{PA}, together with an assumed V_C based on body weight, that the subdivisions of V_v are so distributed that 27% are contained in the pulmonary artery, 15% in the pulmonary capillary, and the remaining 58% in the pulmonary venous beds. These indirect predictions correlate well with our directly measured compartmental volumes, with 28% in the pulmonary artery, 22% in the pulmonary capillary, and 50% in the pulmonary venous segments. In excised lung lobes of dogs, Piiper (2) found that the fractional capillary volume comprised 38% of total blood volume. Since his measurements did not include major extralobar pulmonary vessels, which have been shown to contain a large portion of pulmonary blood volume (11), it is not surprising that the relative contribution of the pulmonary capillary

bed to total blood volume is larger in his preparation. Our relative values also differ substantially from post-mortem studies. For example, Backmann and Hartung (3) found that 53% of total pulmonary blood volume is contained in the capillaries, whereas the rest is evenly distributed in the arterial and venous segments.

The infusion of 5-hydroxy-tryptamine produced only slight decreases in total pulmonary blood volume, and in pulmonary arterial and pulmonary venous blood volume, but a slight increase in pulmonary capillary blood volume. There was also a slight increase in $\dot{Q}_p$. Although Sackner and DuBois (10) were unable to demonstrate a satisfactory relationship between V_V and $\dot{Q}_p$, they found a positive correlation between V_{PA} and $\dot{Q}_p$. Therefore, the decrease in mean pulmonary arterial blood volume, induced by 5-hydroxy-tryptamine in our dogs, may have been partially counteracted by the increase in mean pulmonary blood flow. Also, at a fixed lung volume, an elevation of mean pulmonary arterial pressure by approximately 15 cm H_2O should have resulted in an increase of pulmonary arterial blood volume by nearly 60 ml, assuming a pulmonary arterial compliance of 3.9 ml/cm H_2O (7). The fact that pulmonary arterial blood volume not only failed to increase, but even slightly decreased, strongly supports active pulmonary arterial vasoconstriction by 5-hydroxy-tryptamine, a finding which has been previously reported (12). Mean pulmonary venous volume, on the other hand, showed only a minimal decrease; and, in the individual dogs, we observed variable responses with marked decreases, increases, or no changes. Brody and Stemmler (12) demonstrated in the isolated dog lobe that infusion of low doses (1.5 µg/min/kg) of 5-hydroxy-tryptamine caused vasoconstriction predominantly in the pulmonary artery during <u>forward</u> perfusion, and in the pulmonary veins during <u>retrograde</u> perfusion. High concentrations (5 µg/min/kg) produced vasoconstriction in arteries and veins during both forward and retrograde perfusion. These results indicated that 5-hydroxy-tryptamine is not completely inactivated during one passage through the lung if high concentrations are administered. Our dose of 10 µg/min/kg, which was distributed in the total pulmonary circulation (not just a lobe, as in Brody and Stemmler's experiments), was therefore sufficient to produce consistent vasoconstriction in the pulmonary artery--but only variable responses in the pulmonary veins and, as a secondary passive phenomenon, in the capillaries. The studies of Aviado (13) and Young et al. (14), who used rather high doses (5 - 10 mg, or 100 - 1000 mg in single doses), indicated a vasoconstrictor effect of 5-hydroxy-tryptamine on pulmonary veins when injected into a systemic vein.

Pulmonary $\dot{Q}_c$ was slightly but consistently smaller than $\dot{Q}_p$. Besides the presence of intrapulmonary right-to-left shunts, the rebreathing maneuver (positive pressure breathing), by decreasing cardiac output, may also have been responsible for this difference between $\dot{Q}_p$ and pulmonary $\dot{Q}_c$. No changes in P_{PA} were observed during this maneuver. Since V_C has been shown to correlate with pulmonary arterial pressure rather than cardiac output (15)--the rebreathing technique per se probably did

not alter V_C , and these measurements were therefore comparable to those made during apnea (ether circulation time and double-indicator dilution).

Our experiments demonstrate that the functional volumes of the pulmonary vascular bed can be measured in intact dogs. The preliminary data also suggest that infusion of 5-hydroxy-tryptamine at a rate of 10 µg/min/kg produces pulmonary arterial vasoconstriction with a decrease in pulmonary arterial blood volume, but only inconsistent changes in pulmonary venous and capillary blood volumes. Further studies are planned to evaluate the effect of elevated left atrial pressure and lung inflation on these vascular compartments.

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TABLE 1. FLOW, PRESSURE, AND COMPARTMENTAL VOLUMES OF THE PULMONARY CIRCULATION IN 10 DOGS

Parameters	Mean (±SE)
[10 dogs]	
$\dot{Q}_p$ (liters/min)	2.67 (±0.26)
$\dot{Q}_c$ (liters/min)	2.12 (±0.13)
HR (beats/min)	130 (±9)
$\bar{P}_{PA}$ (cm H_2O)	14.8 (±0.6)
$\bar{P}_{LA}$ (cm H_2O)	5.3 (±1.3)
R_{PV} (cm H_2O/liters/min)	3.5 (±1.8)
PBV (ml)	251 (±26)
V_{PA} (ml)	71 (±10)
V_C (ml)	55 (±7)
V_v (ml)	125 (±20)

TABLE 2. EFFECT OF 5-HT ON PULMONARY CIRCULATION AND RESPIRATORY MECHANICS IN 7 DOGS

Parameters	Control Mean (±SD)	5-HT Mean (±SD)
	[7 dogs]	
$\dot{Q}_p$ (liters/min)	2.68 (±1.22)	2.99 (±1.34)
$\dot{Q}_c$ (liters/min)	2.31 (±0.48)	2.17 (±0.66)
HR (beats/min)	149 (±25)	131 (±23)
$\overline{P}_{PA}$ (cm H_2O)	15.1 (±3.3)	32.1 (±3.5)
$\overline{P}_{LA}$ (cm H_2O)	3.1 (±3.5)	4.6 (±2.7)
R_{PV} (cm H_2O/liters/min)	5.6 (±3.4)	11.2 (±5.7)
PBV (ml)	230 (±108)	217 (±110)
V_{PA} (ml)	58 (±35)	48 (±31)
V_C (ml)	35 (±12)	40 (±32)
V_v (ml)	137 (±85)	129 (±100)
SG_{rs} (liters/sec/cm H_2O/liter)	0.44 (±0.12)	0.16 (±0.08)
C_{st} (liters/cm H_2O)	0.14 (±0.06)	0.13 (±0.03)

Note: 5-HT = 5-hydroxy-tryptamine.

I - V: ABBREVIATIONS, ACRONYMS, AND SYMBOLS

BFS	bronchofiberscope
BSA	body surface area
BTPS	body temperature and pressure, saturated with water vapor
CI	cardiac index
C_{cr}	creatinine clearance
DL	diffusing capacity of the lung
DL/VA	diffusing capacity per unit of alveolar volume
FRC	functional residual capacity
O G_z	supine resting posture
1 G_z	90^{o} head-up (standing) tilt
HR	heart rate
HSG	high-sustained G_z
5-HT	5-hydroxy-tryptamine
i.d.	inside diameter
M-aG	modified USAF anti-G suit
NI	water immersion to the neck
N_2O	nitrous oxide
o.d.	outside diameter
P	probability value
PBV	pulmonary blood volume
PNS	phrenic nerve stimulation
PO	peak systolic output

$\overline{P}_{PA}$	mean pulmonary arterial pressure
$\overline{P}_{LA}$	mean left atrial pressure
$\dot{Q}_p$	pulmonary blood flow
R	respiratory exchange ratio (also: respiratory gas exchange ratio, or respiratory quotient)
R_{PV}	pulmonary vascular resistance
S-aG	standard USAF anti-G suit (CSU-12/P)
SD	standard deviation
SE	standard error of the mean
STPD	standard temperature and pressure, dry
SV	stroke volume
$U_{Na}V$	rate of sodium excretion
$(\dot{V}_A/\dot{Q}_c)$	particular ventilation to perfusion ratio
V_C	pulmonary capillary blood volume
$\dot{V}O_2$	oxygen consumption
V_{PA}	pulmonary arterial blood volume
VTPC	pulmonary tissue plus capillary blood volume
V_v	pulmonary venous blood volume